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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

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December 5, 2012
8:00 a.m.

Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

PANEL MEMBERS:

CLYDE YANCY, M.D.	Panel Chair
DAVID J. SLOTWINER, M.D.	Voting Member
JOHN C. SOMBERG, M.D.	Voting Member
E. MAGNUS OHMAN, M.B., FRCPI, FACC	Voting Member
DAVID C. NAFTEL, Ph.D.	Temporary Non-Voting Member
RICHARD A. LANGE, M.D.	Temporary Non-Voting Member
JOHN W. HIRSHFELD, M.D.	Temporary Non-Voting Member
GREGORY J. DEHMER, M.D.	Temporary Non-Voting Member
DAVID YUH, M.D.	Temporary Non-Voting Member
JOAQUIN CIGARROA, M.D.	Temporary Non-Voting Member
DAVID E. KANDZARI, M.D.	Temporary Non-Voting Member
JEFFREY A. BRINKER, M.D.	Temporary Non-Voting Member
KEITH B. ALLEN, M.D.	Temporary Non-Voting Member
MARC R. KATZ, M.D., M.P.	Temporary Non-Voting Member
JOHN R. DOTY, M.D.	Temporary Non-Voting Member
LAZAR GREENFIELD, M.D.	
DEBRA GATES McCALL	Patient Representative
BURKE T. BARRETT, B.A., B.S., M.B.A.	Industry Representative
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M E E T I N G

(8:08 a.m.)

DR. YANCY: Welcome to today's Circulatory System Device Panel Meeting on Wednesday, December 5th, 2012. My name is Clyde Yancy, and I will be chairing today's session, and I'd like to officially call this meeting to order.

My area of interest is in cardiovascular diseases, and I currently serve as chief of cardiology at Northwestern University in Chicago as a Professor of Medicine with a focus on advanced heart disease, including heart failure, cardiomyopathies, and heart transplantation.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, during Session 1, the Panel will discuss and make recommendations regarding the 515(i) order for external counter-pulsating or enhanced external counter-pulsating systems, one of the remaining preamendment Class III devices. Discussions will involve making recommendations regarding regulatory classification to either reconfirm to Class III or reclassify to Class I or Class II.

Before we begin, I would like to request that our distinguished Panel members, and I do mean that sincerely -- quite a number of you are

friends of ours and we've worked with you in the past -- and FDA staff seated at this table to please introduce yourselves. Please state your name, your area of expertise, your position, and affiliation. And we'll start with Dr. Naftel.

DR. NAFTEL: Good morning. My name is David Naftel. I'm a -- or Naftel. I'm a Professor of --

DR. YANCY: Today it's Naftel.

DR. NAFTEL: Naftel.

(Laughter.)

DR. NAFTEL: I'm a Professor of Biostatistics and Professor of Surgery at the University of Alabama at Birmingham. My area of expertise is biostatistics.

DR. HIRSHFELD: Good morning. I'm John Hirshfeld. I am a Professor of Medicine at the University of Pennsylvania, and I'm an interventional cardiologist by trade.

DR. KANDZARI: Good morning. I'm David Kandzari, and I am an interventional cardiologist. I'm the Director of Interventional Cardiology and the Chief Scientific Officer for Piedmont Heart in Atlanta, Georgia.

DR. ALLEN: My name is Keith Allen. I'm Director of Surgical Research at the Mid America Heart Institute and a practicing cardiothoracic as well as vascular surgeon.

DR. KATZ: Marc Katz. I'm a cardiac surgeon and Chief Medical

Officer at the Bon Secours Heart Institute in Richmond, Virginia.

DR. YUH: Good morning. My name is David Yuh. I'm the Chief of Cardiac Surgery at Yale University, and my areas of interest are in surgical robotics and computational modeling of the heart.

DR. SOMBERG: Good morning. My name is John Somberg. I'm a Professor of Medicine and Cardiology at Rush Medical College and practice cardiology.

DR. OHMAN: Good morning. My name is Magnus Ohman, and I'm an interventional cardiologist from Duke with an interest in clinical trials.

DR. ZUCKERMAN: Good morning. My name is Bram Zuckerman. I'm the Director, FDA Division of Cardiovascular Devices.

MS. McCALL: Debra Gates McCall. I'm the Patient Representative.

MR. BARRETT: Good morning. I'm Burke Barrett. I'm the Vice President of Regulatory and Clinical Affairs at CardioFocus, and I'm the Industry Representative on this Panel.

DR. SLOTWINER: Good morning. I'm David Slotwiner. I'm a cardiac electrophysiologist at North Shore-Long Island Jewish Medical Center and Hofstra Medical School.

DR. GREENFIELD: Lazar Greenfield, vascular surgery, University of Michigan, Professor Emeritus.

DR. DOTY: John Doty, cardiovascular surgeon at

Intermountain Medical Center, Salt Lake City, Utah.

DR. BRINKER: Jeff Brinker, Professor of Medicine and Radiology, Johns Hopkins University. I'm an interventional cardiologist.

DR. CIGARROA: I'm Joaquin Cigarroa, the Clinical Chief of Cardiology at Oregon Health and Science University, Clinical Professor of Medicine, and interventional cardiologist.

DR. DEHMER: My name's Greg Dehmer. I'm an interventional cardiologist, Professor of Medicine, Texas A&M College of Medicine, and Director of the Cardiology Division at Scott and White Clinic.

DR. LANGE: Good morning. I'm Rick Lange. I'm a Professor of Medicine and Vice Chairman of the Department of Medicine at the University of Texas, San Antonio, and just finished therapy from my previous role as an interventional cardiologist.

MS. WATERHOUSE: Jamie Waterhouse. I'm the Designated Federal Officer at the FDA.

DR. YANCY: Again, I'd like to thank the Panel members for being here. I think you can tell as we go around the room that this really is an esteemed Panel, and I'm delighted to work with you today.

If you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Ms. Jamie Waterhouse, the Designated Federal Officer for the Circulatory System Devices Panel, will now make several introductory

remarks. I would request you give her your undivided attention.

MS. WATERHOUSE: The Food and Drug Administration is convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special Government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as

those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contract/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding the 515(i) order for external counter-pulsating or enhanced external counter-pulsating systems, one of the remaining preamendment Class III devices. These systems typically consist of a treatment table, pressure cuffs, and a controller. The discussion will involve making recommendations regarding regulatory classification to either reconfirm to Class III or reclassify to Class I or Class II.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S. Code Section 208.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Mr. Burke Barrett is serving as the Industry Representative, acting on behalf of all related industry, and is employed by CardioFocus.

Unfortunately, due to unforeseen circumstances for which no

time allowed for us to find a replacement, we will not have a Consumer Representative at this meeting.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

For the duration of the Circulatory System Device Panel Meeting on December 5th, Ms. Debra McCall has been appointed as a temporary non-voting member. For the record, Ms. McCall serves as a consultant to the Cardiovascular and Renal Drugs Advisory Committee at the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting. The appointment was authorized by Jill Hartzler Warner, Acting Associate Commissioner for Special Medical Programs, on November 21st, 2012.

Before I turn the meeting back over to Dr. Yancy, I would like to make a few general announcements.

Transcripts for today's meeting will be available from Free

State Court Reporting. Their telephone is 410-974-0947. And information on purchasing videos of today's meeting can be found at the FDA meeting registration desk.

The press contact for today's meeting is Michelle Bolek.

I would like to remind everyone that members of the public and press are not permitted in the panel area, which is in the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with Mr. James Clark at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and any other electronic devices at this time. Thank you very much.

Dr. Yancy?

DR. YANCY: We will now hear from Marjorie Shulman, Director, Premarket Notification (510(k)) Program.

MS. SHULMAN: Good morning. My name is Marjorie Shulman. I'm Director of the 510(k) Program. And we're going to discuss the Device Reclassification Procedures.

So what is the purpose of this Panel meeting? To provide input to FDA on whether sufficient information exists, sufficient scientific evidence exists to develop appropriate special controls to reclassify a preamendment device type from Class III to Class II.

So what is a preamendment device? It's a device that was introduced to interstate commerce prior to May 28th, 1976, which was the enactment date of the Medical Device Amendments.

So what is the classification process? Recent legislation that was just passed this past summer, FDASIA, has affected the classification of medical devices, including Class III 510(k)s, so FDA must now publish a proposed order announcing our proposed classification and seek public comment, hold a panel meeting if classifying or reclassifying a device type, and consider comments and all available information, including panel recommendations, prior to issuing a final order finalizing the classification of the device type.

So what are the device classes? Classification is classified based on the controls necessary, and a device should be placed in the lowest class whose level of control provides reasonable assurance of safety and effectiveness. So Class I is general controls; Class II, general and special controls; and Class III, premarket approval.

So what are Class I devices? Devices for which general controls are sufficient to provide reasonable assurance of the safety and

effectiveness. And Class I devices typically do not require a premarket review prior to being marketed.

So what are the general controls? Prohibition against adulterated or misbranded devices, good manufacturing practices, registration of the manufacturing facility, listing of the device type and recordkeeping and repair, replacement, and refund. So those are an example of Class I controls.

Here are some examples of Class I devices: general cardiovascular surgical instruments, adhesive bandage, manual stethoscopes, crutches.

So what are Class II devices? Class II is for devices that cannot be classified into Class I because the general controls, the ones that were just mentioned, are insufficient to provide reasonable assurance of the safety and effectiveness of the device and for which there is sufficient information to establish special controls to provide such assurance. So Class II devices typically do require premarket notification prior to being marketed, although they can be exempt from 510(k).

So what are the special controls? They include such things as performance standards, postmarket surveillance, patient registries, development and dissemination of guidance documents, et cetera.

What are some examples of Class II devices? Blood pressure cuffs, percutaneous catheters, electronic stethoscopes, vascular graft

prosthesis, ECGs, hemodialysis systems, syringes.

So how are special controls used? For example, PTCA catheters were reclassified from Class III to Class II, into Class II special controls. FDA issued a special controls guidance document to mitigate the risks, and it included such things as biocompatibility testing, bench testing, animal testing, sterility and shelf-life and labeling that included warnings, precautions, adverse effects, et cetera. So these special controls, in combination with the general controls, provide reasonable assurance of safety and effectiveness. So companies must provide evidence in their 510(k) submissions of how the special controls were met.

Class III devices. What are Class III devices? They cannot be classified into Class II because insufficient information exists to determine that the general controls and the special controls are sufficient to provide reasonable assurance of safety and effectiveness, and the devices are life-sustaining and/or life supporting or of substantial importance in preventing impairment of human health or presents potential or unreasonable risk of illness or injury. Class III devices require premarket approval, also known as PMA, prior to being marketed.

So what are some examples of the Class III devices? Endovascular grafts, coronary and peripheral stents, percutaneous heart valves, LVAD devices, et cetera.

So what are Class III 510(k) devices? Those were

preamendment devices -- that's prior to May 28th, 1976 -- where FDA had issued a proposed rule classifying them into Class III; however, no final rule was issued, or a final rule was issued for Class III, but the rule did not contain a date by which the companies were required to submit a PMA. Therefore, these Class III devices are allowed to proceed to market via the 510(k) process until such time either a call for PMAs or the reclassification is finalized.

So what is the reclassification process? FDA may reclassify a preamendment device in a proceeding that paralleled the initial classification proceeding, based upon new information respecting a device either on FDA's own initiative or upon the petition of an interested person. And then the Agency classifies or reclassifies intended uses which have actually been reviewed by the Agency.

So regarding the classification of implants, life support or life-sustaining devices, under 21 C.F.R. 860.93, a panel must recommend for Class III implants life-sustaining or life-supporting devices unless the panel determines that Class III is not necessary to provide the reasonable assurance of safety and effectiveness and can provide reasons for such a recommendation, including references to supporting documentation data, including identifications of the risks to health.

So what will happen after this panel meeting? FDA will issue a proposed order proposing classification of the device and seeking public

comment on the proposal. FDA may propose that the device be reclassified into Class II or I, remain in Class III, call for PMAs, or split the classification based on indications or technology. FDA will consider the available evidence, including the input of this Panel and public comments, and the FDA will issue a final order reclassifying the devices either into Class II or I, Class III, or splitting the classification. If Class II, existing devices will be subject to any identified special controls, and may be -- and may continue to market. Excuse me. If Class III, existing devices will remain on the market but must submit a PMA, a premarket approval application, by a specified time to continue marketing. If the PMA is not approved, devices will be considered misbranded and must be removed from distribution.

Thank you. Any questions?

(No response.)

MS. SHULMAN: Thank you.

DR. YANCY: Thank you, Ms. Shulman. I'd like to thank her for the presentation and once again survey the Panel to see if there are any questions for Ms. Shulman regarding device reclassification.

(No response.)

DR. YANCY: If there are not, then at this point, we are several minutes ahead of time -- thank you -- and I'll invite FDA to begin their presentation, please.

DR. WU: Go ahead and bring the slides up. Good morning.

My name is Changfu Wu. I'm a biomedical engineer and lead reviewer for this external counter-pulsating device classification panel.

You have heard Marjorie's presentation about the 515(i) process. I want to reiterate some of the main points as related to the ECP devices. The ECP devices are one of the remaining preamendment Class III medical devices.

For Class III devices, premarket application, PMA, is typically required. However, ECP devices are currently marketed through the 510(k) process, which is typically reserved for a Class II device. So we need the Panel's input on how to address this issue.

Throughout this morning, the FDA team will first present the clinical evidence for ECP devices and then ask the Panel to weigh in on FDA's recommendation on whether to down-classify ECP devices to Class II, requiring 510(k)s, or to keep them as Class III, requiring PMAs.

Here's the outline for the FDA presentation. The FDA presenting team consists of myself, Dr. Dale Tavris, and Dr. Suzanne Baron. I'll first introduce the device and then give the podium to Dr. Tavris and Dr. Baron. Dr. Tavris will discuss the methodology used in the systematic literature search and provide an overview of the literature for the effectiveness of ECP devices in the treatment of angina. Dr. Baron will look at some of the clinical studies in more detail and provide the clinical perspectives. In the end, I will return to present the FDA recommendation.

As is currently defined in the regulation, an ECP device is a non-invasive device used to assist the heart by applying positive or negative pressure to one or more of the body's limbs in synchrony with the heart cycle. It typically consists of a treatment table, a set of inflatable pressure cuffs, and a control console. During treatment, the pressure cuffs are wrapped around the calves, the lower and upper thighs. Controlled by the control console, a pneumatic circuit inflates the pressure cuffs during diastole and deflates them during systole.

The inflation of the cuffs occurs sequentially starting from the cuffs and then moving proximally, which creates an arterial retrograde blood flow towards the heart and increases blood flow to the coronary arteries; and at the same time, increases the volume of venous blood return to the right heart, providing greater filling of the ventricle for injection.

As I have mentioned earlier, the ECP devices were one of the preamendment devices when the Medical Device Amendments to the Federal Food, Drug and Cosmetic Act was enacted in 1976. The initial classification panel recommended Class III classification for ECP devices, citing three reasons: (1) The device is life-supporting and is potentially hazardous to life or health even when properly used; (2) General controls alone is insufficient for performance control; and (3) There's insufficient information to establish a performance standard to provide assurance of the safety and effectiveness of the device.

Following the panel recommendation, FDA published a final rule in 1980 classifying ECP devices as Class III. However, an effective date for the call for PMA was never implemented. On April 9th, 2009, FDA issued an order requesting safety and effectiveness information for the ECP devices to determine whether the classification for the device should remain Class II -- should remain as Class III and require a PMA submission or be revised into Class II with special controls or Class I with general controls.

Following the order, five ECP device manufacturers responded. They collectively hold a total of 18 out of the 27 cleared 510(k)s. One manufacturer did not know what classification is appropriate and left the decision to the FDA. Four manufacturers recommended reclassification to Class II.

Over the years, the indications for use cleared for ECP devices have expanded to include a long list of cardiac indications, peripheral vascular indications, and musculoskeletal indications. The cardiac indications include: angina, myocardial infarction, cardiogenic shock, and heart failure, et cetera.

In preparation for this panel, FDA examined the clinical evidence for ECP devices. Since there have been no IDE studies or 522 postmarket surveillance studies, we relied on MDR reports and literature.

In all, there are 54 MDR reports, including 5 deaths, 47 injuries, and two others. Three of the deaths were possibly device-

related. The most frequent injuries were breathing difficulties, pulmonary edema, and exacerbation of heart failure. Although accurate adverse events rate cannot be established based on the MDR reports, the total number of 54 adverse events over the last 13 years suggests that the overall adverse events rate is low, as compared with about 18,000 to 20,000 patients with coronary artery disease being treated annually in the U.S.

I now turn the podium to Dr. Dale Tavris to talk about how the systematic literature review was conducted and to provide an overview of the literature for the effectiveness of ECP devices in the treatment of angina.

Dr. Tavris?

DR. TAVRIS: Thank you, Dr. Wu.

Good morning. My name is Dale Tavris, and I'm a physician/epidemiologist in the Division of Epidemiology in the Office of Surveillance and Biometrics. My presentation will begin by describing the methodology used in the Division of Epidemiology's literature search on the performance of ECP for FDA-cleared indications. I will then focus on the results of the literature search relating to the effectiveness of the ECP in the treatment of angina pectoris.

Is this -- oh, okay. Okay. Our initial identification of articles was conducted on March 15th, 2012, using PubMed. The key search words were "external" and "counter-pulse," short for counter-pulsation. An article

had to contain both of those words in order to result in a hit.

Our computer search of the literature in PubMed initially identified 301 articles. Inclusion/exclusion criteria included: The article had to be written in English; it had to be either a randomized controlled trial or an observational research study with a sample size of at least 50. In other words, articles that did not depict research studies, such as reviews, editorials, case reports or case series were excluded. The primary search of the research had to be the evaluation of the effectiveness of ECP for the specified indication.

After review of the abstracts, applying the inclusion/exclusion criteria and eliminating duplicate information, we ended up with 32 articles for our review. These 32 articles involved the use of ECP for the treatment of angina, myocardial infarction, and congestive heart failure.

The remainder of my presentation will be confined to the presentation of results and discussion of the literature review dealing with the effectiveness of ECP in the treatment of angina. This topic was chosen for my presentation because angina is the only indication for ECP for which extensive literature exists regarding its effectiveness. Dr. Baron will later discuss the literature regarding the other indications.

Of the 32 articles meeting the inclusion/exclusion criteria for our literature search, 26 of them involve the use of ECP in the treatment of angina. I will now focus on those articles. Those 26 articles involved four

randomized controlled trials, 21 observational studies, and one meta-analysis, which included 13 observational studies.

You can see from this slide that the timeframe for the articles we reviewed ranged from 1998 to close to the present. Sample sizes of greater than 1,000 were used for most of the observational studies, many of which involved the large international registry, while the randomized controlled trials were generally much smaller, the largest involving 139 subjects. All but two of the observational studies involved only self-controls, that is, a comparison of outcomes before and after ECP treatment. All of the RCTs used sham ECP treatment in the control group.

The articles that we reviewed contained different types of evidence of effectiveness of ECP in the treatment of angina, including improvement in Canadian Cardiovascular Society anginal class, other measures relating to a decrease in chest pain, improvement in exercise duration, improvement in quality of life, and in increase in myocardial perfusion.

Improvement in Canadian Cardiovascular Society anginal class was assessed in 20 of the 22 observational studies but in none of the four RCTs. Seventeen of those 20 studies assessed improvement immediately post-ECP treatment. Of those, the studies showed a range of effectiveness ranging from improvement in 73% to 88% of subjects immediately post-ECP. Regression to a worse CCS class was rare to nonexistent. Twelve of the

studies used the International ECP Patient Registry as the primary data source.

Most of those studies assessed various subgroups of patients for ECP effectiveness. All subgroups in all of the studies except for one showed improvement in CCS angina class in at least 65% of subjects, and improvement in all of the subgroups was statistically significant. The one subgroup that did not demonstrate improvement in at least 65% of subjects was the subgroup of those who did not complete treatment. That subgroup showed improvement in only 22% of subjects.

Several studies also looked at long-term reduction in CCS class. All showed statistically significant improvement. Of those, two studies showed improvement in 73 to 77% of subjects at six months. Four studies showed improvement in 61 to 78% of subjects at one year. One study showed improvement in 29% of subjects at two years, and one study showed improvement nearly maintained by three years in 78% of subjects.

Other direct measures of decreasing angina pain included assessment of anginal frequency, frequency of nitroglycerin use, peak anginal pain, and time to first anginal episode. All of these measures demonstrated statistically significant improvement.

Four studies assessed the frequency of angina. Each of these four studies showed statistically significant improvement in angina following ECP treatment. One of those studies showed statistically significant

improvement over baseline as long as three years following treatment. One compared ECP with percutaneous coronary intervention, with statistically significantly more favorable results for PCI. Angina frequency was 73% in the ECP group compared to 44% in the PCI group over the period of this study.

One observational study demonstrated the following improvement over time: At baseline, the mean number of angina episodes was seven per week. Immediately post-ECP treatment, angina frequency declined to one episode per week. And by one year, the frequency of angina episodes per week rose to two, slightly over the immediately post-treatment results but still far less than angina frequency at baseline.

Five studies assessed the frequency of nitroglycerin use. Four of the five were observational studies, and all showed a statistically significant decrease in nitroglycerin use. One of those studies involved a three-year follow-up and showed the decrease in nitroglycerin use maintained at three years. One of the studies was a randomized controlled trial. That study showed a statistically significant decrease in nitroglycerin use post-ECP compared to sham-treated controls.

Exercise duration provides good evidence of improvement in angina because angina pain inhibits the ability of people to maintain exercise. Statistically significant improvement in exercise duration was shown in five studies. Three were observational studies and two were RCTs,

which included one with statistically significant improvement in exercise duration compared with sham-treated controls.

One RCT evaluated health-related quality of life. In this double-blinded study, improvement in ECP subjects compared with sham-treated controls was shown in three of the four quality of life scales that were evaluated at one year. Statistically significant improvement was shown in the social, pain, and cardiac scales compared to the controls. Significant improvement was also shown in the physical scale over time, but the difference was not statistically significant compared to the sham-treated controls.

Statistically significant improvement in myocardial perfusion was shown in three studies using different methods, including radionuclide stress testing, radionuclide perfusion treadmill stress test, and myocardial oxygen consumption.

A potential explanation for the increase in myocardial perfusion was shown by another study which evaluated blood flow in the collateral blood vessels. That study showed an increase in the collateral flow index in ECP-treated subjects from 0.125 to 0.174. A much smaller improvement in collateral flow index was shown in the sham-treated controls. The difference was statistically significant at the p=.0009 level.

The main limitation of RCTs is that they may not be conducted in ways that simulate real-world conditions. When that is the case,

treatments may perform less well in the real world than they do under the generally highly controlled conditions of an RCT.

The main limitation of the observational studies used in this review was the lack of an external concurrent control group. The fact that all but two of them used no external concurrent control group means that one must consider the possibility that improvements demonstrated in these studies reflected the natural history of the disease or other treatments rather than the effects of ECP.

In that regard, it is worth noting that the concurrent use of other treatments was not assessed in the observational studies. However, the fact that the subject population in all of these studies was patients with chronic and stable angina in many or most cases refractory to other treatments for their disease mitigates against the possibility that the natural history of the disease or other treatments were responsible for the large improvements in clinical status demonstrated in these patients.

I believe that the many strengths of these study findings as a group more than counterbalance the limitations. The findings of beneficial effects in these studies were remarkably consistent. Statistically significant positive effects were demonstrated in every study that met the inclusion criteria for our literature review. Many different measures of effectiveness were assessed, and all demonstrated improvement in subjects from baseline to post-treatment in the observational studies, and in the RCTs, significantly

better results in ECP-treated subjects than in controls.

The findings of beneficial effects in the observational studies were highly consistent, not only among each other, but also with the results of the RCTs. Because of that, the intrinsic limitations of RCTs were compensated for by the observational studies, and most of the intrinsic limitations of observational studies were compensated for by the RCTs. The beneficial effects were generally of large magnitude, which makes it much less likely that confounding variables, the natural history of the disease or the concurrent use of other treatment in the observational studies would have accounted for them. And every subgroup of patients assessed in these studies was found to exhibit beneficial effects.

Lastly, it should be noted that only two of the studies in this literature review assessed ECP treatment compared to another treatment for angina. The others compared ECP treatment with no treatment at all, that is, the self-controls, or only with placebo-treated controls in the RCTs.

Dr. Baron will now discuss some of the studies used in this literature review in greater detail, including a discussion of safety issues, as well as the much smaller body of evidence relating to the effectiveness of ECP for other indications.

DR. BARON: Thank you, Dr. Tavris. My name is Suzanne Baron. I'm an interventional cardiologist and a medical staff fellow at the FDA, and I'm going to be providing a clinical interpretation of the

literature on ECP for various indications.

So to understand what conditions ECP might be useful for, it's reasonable to review the proposed mechanisms for the physiological effects of ECP. So as mentioned earlier, with the decrease in volume in the vascular bed during systole, the heart may experience a decrease in afterload, which translates to decreased cardiac workload, decreased oxygen consumption, and, hence, decreased ischemia.

Another proposed mechanism for the cardiac effects of ECP is an increase in coronary blood flow, which is triggered by the increase in diastolic pressure associated with ECP. In this proof-of-concept study, 10 patients underwent left heart cath both at baseline and during ECP. While ECP was being performed, both central aortic pressure as well as intracoronary pressures, as measured by a doppler flow wire in the coronary artery, were recorded simultaneously. In this representative tracing, you can see that there was a substantial increase in both diastolic pressures in the aorta as well as in the coronary artery. And this actually translated into an increase in coronary flow of 28% during ECP, as measured by TIMI frame count.

By increasing coronary blood flow, we can get one of two effects. First, we may see an increase in the flow down preexisting collaterals to the diseased myocardium.

To evaluate this hypothesis, researchers took 20 patients with

chronic stable angina, and they randomized them to a course of ECP or to a sham procedure. In an effort to evaluate changes in coronary collateral flow, they chose to measure the collateral flow index in the artery with the most severe stenosis both before and after treatment. They did this by advancing a pressure wire through a balloon catheter down the artery distal to the stenosis. The balloon was inflated proximal to the stenosis, and the pressure in the artery was measured distally. After obtaining the distal pressure during balloon occlusion as well as the mean aortic pressure and the CVP, they were able to calculate the collateral flow index, as defined by the equation noted here.

This graph demonstrates the overall observed results. Patients who received ECP had, on average, a significant increase in their collateral flow index, as compared to patients who received the sham treatment.

In addition to improving collateral flow, increased coronary blood flow may also lead to an increase in shear stress that is seen by the coronary arteries, and this can lead to alterations in endothelial function. Series of small studies in humans as well as in animals have found an increase in nitric oxide production and a decrease in endothelin-1 levels after ECP, and this can lead to vasodilation in the collaterals. Furthermore, studies in a canine model of ischemia have found that ECP can lead to an increase in VEGF as well as fiber blast growth factor, and these are

molecules that can promote angiogenesis in the ischemic myocardium.

So by understanding the possible mechanisms by which ECP works, we can then break down the proposed indications for ECP by theorized mechanism. By improving coronary blood flow and thereby decreasing cardiac ischemia, ECP could be used to treat chronic stable angina or acute coronary syndromes. By decreasing afterload, ECP could be used to treat CHF or cardiogenic shock. And although I didn't discuss this much, by simulating a passive exercise-like activity in the legs, ECP could be used to treat conditions relating to peripheral arterial disease.

The majority of the clinical evidence in the literature is related to the use of ECP in its treatment of chronic stable angina. As we all know, chronic stable angina is a common condition affecting an estimated 9.8 million patients in the U.S. each year. There are a range of treatments, including antiplatelet agents, beta blockers, calcium channel blockers, nitrates, ranolazine, lifestyle modifications such as exercise, weight loss, and smoking cessation. And ECP is another possible treatment for this condition as well.

There have been four RCTs that have examined the question of the use of ECP in patients with chronic stable angina. The largest RCT is the MUST-EECP trial, which was published in *JACC* in 1999. In this multicenter, prospective, blinded, randomized trial, 139 patients with chronic stable angina were randomized to either 35 hours of ECP over a 4- to 7-week

period or to a sham procedure. To be included into the study, patients had to have angina symptoms of CCS Class 1 through 3, there had to be documented evidence of CAD, and they had to have a baseline exercise treadmill test that was positive for ischemia.

At each session of ECP or sham ECP, the patients would be asked about the number of angina episodes they experienced, and within one week of course completion, patients underwent a post-treatment treadmill test. Differences in angina frequency from the start to the end of the trial were compared between the two groups, and changes in exercise duration and time to ST segment depression from baseline to post-treatment treadmill test were also compared between the two groups.

The study was designed to detect a 45-second difference in exercise duration between the two groups with a power of 80% and an alpha of 0.05.

The baseline characteristics of the patients in the MUST-EECP trial are summarized here in Table 1: 71 patients received ECP; 66 patients received the sham treatment. Patients were remarkably similar, with the only significant differences between the groups being that the ECP group had a higher percentage of prior MI and a longer duration of angina.

I do want to bring your attention to two categories of baseline characteristics. First, with regards to prior revascularization, between 38 and 47% of patients in both groups had undergone CABG, and between 33

and 35% of patients in both groups had had a prior PCI. Keeping in mind that this study was not conducted during the stent era, I suspect that if this trial were repeated today, these numbers would certainly be higher, and stents would be used.

Second, with regard to medical regimen, you can see here that a majority of patients were on aspirin, nitrates, and beta blockers, and about 50 to 60% of patients were on calcium channel blockers and lipid-lowering regimens. That said, there is no description of patients' blood pressure control, heart rate control during the time period of the trial, and there's no description of lifestyle factors, such as smoking, exercise regimens, BMI, so it's hard to know if these numbers represent maximal medical management.

And, lastly, ranolazine was not being used at that time, and so it wasn't available to these patients.

Taken together, these characteristics of the MUST-EECP study population will make it somewhat difficult to generalize the results to a contemporary population of chronic stable angina patients today.

With regards to the primary endpoint of exercise duration, both patients in the sham ECP group as well as the active ECP group had a significant increase in their exercise duration. However, the between group difference was non-significant at 0.31. And this suggests a possible placebo effect of ECP.

With regards to secondary endpoints, there does appear to be

an effect here. There was no significant change in time to ST segment depression in the sham ECP group, but patients in the ECP group did have a significant increase in their time to ST depression of 42 seconds on average. Here, the between group difference was significant, with a p-value of 0.01. And with regards to anginal frequency, in the intention-to-treat group, there was an improvement in anginal counts in the ECP group, as reflected by a decrease in the median reported counts by 20%. This was also significant at a p-value of less than 0.05.

So taken together, the findings of an improvement in anginal episodes as well as an improvement in time to ST depression are certainly suggestive of benefit. But the study wasn't powered to detect differences on these endpoints. And, furthermore, there was no between group difference in the primary endpoint of change and exercise durations, so the study didn't meet its primary endpoint.

There were three other small RCTs or analyses besides the MUST-EECP trial that have investigated the effects of ECP in stable angina patients. Two of these studies were primarily physiological investigations. As described earlier, there was a small study of 20 patients which found a significant increase in coronary collateral flow in ECP-treated patients. A second small study randomized 42 patients to a full course of ECP or sham treatment and then used ultrasound to measure differences in blood flow in the brachial and femoral arteries. Patients who received ECP had a 30 to

50% increase in peripheral arterial flow-mediated dilation, and they were also noted to have lower levels of endothelial-derived pro-inflammatory cytokines such as TNF-alpha and CRP.

The final study was an analysis of a subset of 71 patients from the MUST-EECP study. All patients in the study were contacted at one year, and data from 71 of the original 139 patients were obtained. At one year, patients who received ECP had maintained improved quality of life on all parameter scales of the SF-36 while patients receiving the sham treatment maintained improved quality of life only on the physical functioning scale. It should be noted that this analysis was not controlled for any confounding change in medical treatments or revascularization status during the interim time between ECP treatment and one-year follow-up.

While the RCTs may not have provided us with a clear conclusion regarding the effectiveness of ECP in patients with stable angina, there have been many observational studies that have looked at this question. Overall, results from the observational studies have suggested that ECP is associated with an improvement in exercise duration, time to myocardial ischemia, quality of life, and anginal frequency and severity.

Of the observational analyses, many of these studies were derived from the International Enhanced External Counter-Pulsation Registry, or the IEPR. This registry has followed over 1,000 patients with stable angina as well as other conditions who have been treated with ECP.

In this representative paper, researchers describe the effects of ECP on 1,427 patients with stable angina who were treated with a full 35-hour course of ECP.

And as you can see in this figure, patients demonstrated an improvement in CCS anginal class immediately after ECP. And in just over 1,000 who were interviewed three years later, this effect in improvement in CCS class does appear to be sustained. With that said, this study was not controlled for changes in revascularization status or changes in medication regimen during that three-year time period. So whether ECP is solely responsible for this type of durable effect is questionable.

So, in summary, data derived from RCTs in observational studies are suggestive of some benefit of ECP. However, as I have alluded to, there's limitations to both sets of the data, and they need to be considered before reaching a clinical conclusion regarding the utility of ECP in this patient population.

Firstly, and perhaps most importantly, most of the observational studies made minimal to no adjustment for possible other factors that might have affected results. In particular, factors such as changes in anti-anginal regimens or revascularization procedures were not protocolized during these studies, nor were they adjusted for by statistical analyses. So it's difficult to know if ECP was definitively responsible for the observed improvement in angina or whether these symptomatic changes

were due to changes in other meds or to other procedures.

Secondly, the observational body of literature incorporates a rather large but heterogeneous patient population with no concurrent controls. Some studies included patients who had revascularization options; others did not. Patients were on various medical regimens, with little description of the drugs that were used. Blood pressure, heart rate control were not described.

Furthermore, medical therapy and revascularization techniques have advanced since most of these studies were performed. Those patients were included in these studies and considered refractory or unrevascularizable at the time. They're likely different from the refractory or the unrevascularizable patients of today. Today we have different drugs on the market to treat angina as well as more advanced revascularization techniques, and that may allow for more patients to undergo procedures and to achieve better revascularization outcomes.

Thus, while the large breadth of observational studies on this subject have shown a benefit to ECP, the results should be interpreted while keeping these limitations in mind.

Data derived from RCTs are also suggestive of benefit, but limitations exist here as well, mainly that the body of RCTs on the subject only incorporated one clinical study in a substudy analysis of 139 patients in which the primary endpoint wasn't reached. Furthermore, no studies that

have been performed to date, observational or RCT, have demonstrated a clear benefit of ECP over other proven medical treatments, such as nitrates, calcium channel blockers, optimal heart rate/blood pressure control, ranolazine, weight loss, smoking cessation, and an exercise program.

So while absolute effectiveness of the device might be in question, there is little evidence in the literature to suggest that ECP is harmful in this population. The most common device-related adverse reactions reported include skin abrasions and temporary leg or back discomfort. So it's likely a safe device.

We believe that a large body of observational studies and a limited number of RCTs provide sufficient evidence to suggest that ECP might be beneficial, and it's likely safe. But given the limitations described herein, it shouldn't be used in place of or in preference to another strategy which has been proven to be effective through rigorous testing in larger-scale RCTs, and hence should be reserved for those patients who have exhausted other options for treatment of their angina. And the recent 2012 update on ACC/AHA guidelines on the treatment of stable ischemic heart disease are concordant with this assessment and have given ECP a Class IIb recommendation for patients with stable angina who are refractory.

Turning now to the indication of CHF. As we know, CHF is another common condition that's affecting 5.7 million patients in the U.S. It's caused by a wide variety of etiologies and can present with many varying

symptoms. We also have a range of treatments for CHF: ACE inhibitors, aldosterone antagonists, beta blockers, diuretics, digoxin, and CRT-ICD device therapy. ECP has been proposed to be another treatment for CHF.

The effect of ECP on CHF was evaluated in a single RCT known as the PEECH trial, which was published in *JACC* in 2006. In this multicenter, prospective, randomized trial, 187 patients with an EF less than 35% and New York Heart Association Class II to III symptoms were randomized to either meds alone or 35 hours of ECP over a 7- to 8-week period. Meds included beta blockers and ACE inhibitors. However, doses and stability of the treatment were not mandated by the protocol. Patients and caretakers were obviously not blinded in this trial. However, the sponsor, the core labs, and the endpoint committees were blinded to treatment group when adjudicating outcomes.

Co-primary outcome measures were the percentage of patients with a 60-second or more increase in exercise duration; and the percentage of patients with at least a 1.25 cc/kg/min increase in peak VO_2 at six months. The study was designed to have 90% power and was considered positive if there was a statistically significant difference in either primary endpoint at a .025 level or in both endpoints at the .05 level.

A total of 187 patients were enrolled, with 93 patients in the ECP group and 94 patients in the control group. There were no significant differences between the two groups in either demographics or reported

medication regimens. The mean EF in both groups was about 26%; 70% of patients had an ischemic etiology to their heart failure; 75% of patients were taking ACE inhibitors; 85% were taking beta blockers. There was no description of the diuretic dosing or other therapies that patients were taking during the study, and the protocol did allow for medication regimens to be changed during the study duration at the discretion of the caretaker.

Here, the study did meet its primary endpoint. 35.4% of patients who received ECP had an increase in exercise duration of greater than 60 seconds from baseline at 6-month follow-up as compared to 25.3% of patients not receiving ECP. This was a statistically significant at .016. That said, there was no statistically significant in the number of patients who had an increase in peak VO_2 of greater than 1.26 cc/kg/min from baseline obtained between the two groups.

While this study is suggestive of a benefit of ECP and CHF patients, it's small, with a demonstration of a modest effect. And, again, it's not clear whether these changes could have been explained by differences in medication regimens or other confounding variables.

There were only two observational cohort studies that were identified regarding the use of ECP in the treatment of heart failure. In these two small studies, a total of 195 patients with ischemic heart failure were treated with courses of ECP. In general, the results were suggestive of a possible benefit in the treatment of heart failure, with improvement seen

in New York Heart Association class, ejection fraction, hospital admission rates, and BNP levels. But, again, studies were small, there was no comparator group, no adjustment for changes in medication regimen that may have accounted for these findings.

So, in summary, there's limited evidence to suggest that ECP treatment in the CHF population is effective. In contrast to the data on stable angina, there's not a large body of observational evidence to suggest a likely benefit of ECP for CHF patients, and the results of a single RCT with modest results are not enough to draw a clinical conclusion that ECP is effective in this population.

Furthermore, there's a question as to whether this device might lead to episodes of CHF exacerbation in patients with heart failure. As discussed earlier, by increasing venous return back to the heart through lower extremity compression, the heart may see an increase in preload. And a small study of 10 patients that looked -- used a PA line to evaluate the hemodynamic effects of ECP confirmed this. They saw an immediate increase in RA pressure as well as pulmonary capillary wedge pressure. And, clearly, in patients with heart failure, this may be an undesired effect.

In addition, an observational study and a registry have suggested that there may be an increased risk of CHF exacerbations with ECP treatment in patients who have a history of CHF. This trend was also reflected in the MDR reports in which the majority of MDRs were related to

CHF exacerbation, pulmonary edema or breathing difficulties. But that said, the overall number of MDR reports was very low, so it's likely that ECP doesn't lead to CHF exacerbations in all patients with CHF, but more data is needed to define those patients at risk for an exacerbation with ECP treatment.

Indeed, further studies are needed before this device can be considered effective and safe in this population. And, again, in concordance with the conclusions of this literature review, the ACC/AHA guidelines on management of congestive heart failure make no recommendation on the use of ECP in the management of CHF.

And, lastly, ECP has been proposed to treat other cardiovascular conditions as well, including ACS, cardiogenic shock, and conditions related to peripheral arterial disease. Data on both effectiveness and safety of ECP for these indications is severely lacking. A literature search returned one to two manuscripts per indication, and none of these were from the contemporary era. Given the lack of data regarding the use of ECP in these conditions, ECP cannot be recommended for these conditions until further studies are done.

So, in summary, then, despite the described limitations of the literature, the totality of the data has led to the clinical conclusion that ECP may be beneficial and is likely safe in patients with chronic stable angina, but it should be reserved for patients who have exhausted other proven options,

i.e., those patients who are not revascularization candidates and who are refractory to contemporary optimal medical therapy.

Further studies are needed to determine the effectiveness and safety in patients with CHF, ACS, cardiogenic shock, and conditions related to peripheral arterial disease.

I will now turn the podium back over to Dr. Wu, who will present the FDA's recommendations regarding classifications of the ECP device.

DR. WU: You have just heard the clinical evidence related to safety and effectiveness presented in literature for ECP devices. With regard to risks to health of ECP devices, FDA identified four risks, including cardiac arrhythmia associated with excessive electrical leakage current; trauma to the limb associated with improper mechanical design; ineffective cardiac assistance associated with improper synchronization with the cardiac cycle; and the failure to identify correct patient population.

The first three risks were identified by the original panel, and FDA believes they are still relevant. The fourth risk is newly identified based on MDR reports and recommendation by the industry.

Use of the device on patients with certain comorbidities might lead to adverse events such as exacerbation of heart failure. Patients with congestive heart failure represent over half of the MDR reports.

Based on the totality of the clinical evidence we just

presented, FDA recommends that 21 C.F.R. 870.5225 be split based on the proposed indications of the ECP devices, to include both a Class II with special control and Class III requesting PMA application. The Class II indication is for the treatment of chronic stable angina that is refractory to optimal antianginal medical therapy and without options for revascularization. The Class III indication is for all other intended use.

It should be noted that FDA is not recommending any changes to Part (a) Identification of the regulation.

For the proposed Class II indication, FDA recommends the following special controls:

1. Nonclinical performance evaluation of the device must demonstrate a reasonable assurance of safety and effectiveness for applied pressure, synchronization of therapy with the appropriate phase of the cardiac cycle and functionality of alarms during a device malfunction or abnormal patient condition;

2. Reliabilities of the mechanical and electrical system must be established through bench testing under simulated use conditions and matched by appropriate maintenance schedule;

3. Software design and verification/validation must be appropriately documented;

4. The skin contacting components of the device must be demonstrated to be biocompatible;

5. The appropriate analyses and testing must be conducted to verify electrical safety and electromagnetic compatibility of the device; and

6. Labeling must include a detailed summary of the device-related and the procedure-related adverse events pertinent to use of the device.

It is worth noting that under this paradigm, FDA generally will not get clinical data.

This concludes FDA's presentation.

DR. YANCY: Thank you. I would like to thank Dr. Wu, Dr. Tavris, and Dr. Baron for very well-presented information that helps inform our deliberations.

I'd like to request that the graphic go back to slide 55 so that this can be up for the purposes of the Panel discussion. Thank you.

Does anyone on the Panel have at this time any brief or clarifying questions for FDA? Recognize that there will be time later this morning during our deliberations to specifically reengage the FDA presenters.

Yes, David, Dr. Yuh?

DR. YUH: Thank you very much, Dr. Yancy. David Yuh here.

For Dr. Tavris, amongst the studies that showed durable benefit for EECP, how many of those were RCTs? Was it just the one, or were there subsections of the other or smaller trials that also demonstrated

that?

DR. TAVRIS: There were four RCTs in the literature review of 26 studies that I discussed. If you're talking about -- each of the RCTs demonstrated statistically significant improvements in the ECP-treated controls compared to sham-treated -- I mean the ECP subjects compared to sham-treated controls.

If you're asking about durable benefits, the randomized controlled trials were all of short duration whereas many of the observational studies were much of longer duration.

DR. YUH: Thank you.

DR. ZUCKERMAN: Dr. Yuh, if you have further questions about that, on FDA slide 16, Dr. Tavris has the four RCTs listed with their sample sizes.

DR. YANCY: Dr. Sonemblak [sic]?

DR. SOMBERG: Have there been any recalls with any of these iterations of the device, and do you have a table where there are -- I mean, there are a lot of deaths that were always reported with things, but deaths related to the device, looking at serious adversities, hospitalizations, or deaths?

DR. WU: There was one recall associated with the ECP devices historically. For death, all together five deaths in MDR reports, and I think two of them were, based on the description in the MDR reports, so they

were ruled out. They have nothing to do with the device, based on the manufacturers' investigation. But three of them, there's no -- whether they're related to the device or the therapy or not cannot be ruled out clearly, so --

DR. YANCY: I would call your attention to slide 11 in the FDA presentation. That is a summary of the MDRs that presumably are from the MAUDE database. Approximately 20,000 uses of the technology per year, with 54 MDRs since 2001, five deaths, three possible device-related, and 47 injuries.

Dr. Ohman?

DR. OHMAN: So I have a question for Dr. Tavris and Dr. Baron. I realize that we're talking about angina, but I'm also less certain of what definitions of angina we're talking about. And, in particular, when we talk about ischemic cardiomyopathy with shortness of breath, it's angina-equivalent. I'm wondering if you can give us some guidance what your chart review really indicated to be angina.

DR. TAVRIS: Well, as you know, there were several studies involved, and I -- my recollection is that the -- that they involved the typical definition of angina, that is, involving chest pain of -- you know, characterized as cardiac chest pain, without further elaboration of other systems.

DR. YANCY: Dr. Cigarroa, Dr. Lange, and Dr. Allen?

DR. CIGARROA: Any insights in the group of patients in the randomized clinical trials or in the observational trials, was there any discussion of patients with either, A, clinical symptoms consistent with congestive heart failure or, B, depressed left ventricular systolic function, given what we see in the physiologic studies of an elevation in right atrial pressure and pulmonary capillary wedge as potentially being harmful for the treatment of "angina"?

DR. TAVRIS: Several of the observational studies involved, as I said, a large international registry, and those studies involved generally over 1,000 patients, and they looked at various subgroups. And one of the subgroups that was looked at was patients who had angina and concurrent congestive heart failure. And there was substantial improvement in that subgroup of patients with congestive heart failure.

With regard to safety concerns, most of the studies that I discussed involved -- well, looked primarily at effectiveness rather than safety, but some of them did look at safety issues, too. And none described significant safety concerns.

DR. BARON: And for the randomized controlled trials, the people who had EF less than 30% in all four trials were excluded from the trial, so it's hard to say from there.

DR. YANCY: Dr. Lange?

DR. LANGE: Three questions. The first is for the MDRs, the

patients that reported breathing difficulties, pulmonary edema, exacerbation of heart failure, were these patients being treated for angina or heart failure? Do we know?

Second is there was a concern expressed about cardiac arrhythmias, and have they actually been reported with this device?

And the last is other than the EKG recording these, are there any electrical parts of this equipment that comes in contact with the patient?

DR. WU: So for the first question, we do not know based on the descriptions in the MDR reports.

For the second question, it's about the cardiac arrhythmia, right? Well, some of the patients -- I think -- let me just repeat what the definition was for the cardiac arrhythmia. It was associated with the excessive electrical leakage current. It is not related to the patient's underlying condition. But in MDR reports, we do see some occurrences of atrial fibrillation in those patients. Many of them occurred during the treatment.

And the last question is about whether there's any electrical leads connected to the patients. The EKG leads will be connected to the skin because the whole therapy is -- the activation and deactivation of the pressure is triggered by the cardiac cycle.

DR. YANCY: Dr. Allen?

DR. ALLEN: Hi, a number of you made specific references that you seemed to be impressed by the fact that we had randomized controlled trials with blinded, sham controls. And in one study, I think you even said it was a double-blinded sham control. Can you clarify for me how you have a blinded sham control when patients would obviously, number one, know that they have the compression devices placed, and they would certainly know that they were being inflated or not?

DR. TAVRIS: Well, as far as controlling -- well, as far as blinding of the patients is concerned -- well, they weren't all double-blinded. The double-blinded study that I referred to -- well, for example, one study involved a treatment with the same type of machine that looked like the ECP equipment but used much less pressure.

DR. ALLEN: That was one of the three, or one of four, but three of the randomized trials you said were blinded sham. One used less pressure.

DR. TAVRIS: I said they were compared to sham controls. I don't remember specifically what the -- what treatment was given in each of them.

DR. YANCY: Dr. Kandzari?

DR. KANDZARI: Thanks for your presentation. This is a question to Drs. Tavris and Baron. Dr. Tavris, you presented the data that represented clinical trials experience over approximately 11 to 12 years.

And over the course of that time, I have two questions for you. One is did the technique change in the performance of EECP over that time period? And, secondly, have there been any iterative device changes, any meaningful changes, to the technology over that time period?

DR. TAVRIS: I'm not aware of any.

DR. BARON: Neither am I.

DR. WU: So I think they -- let me check the numbers. I thought --

DR. KANDZARI: And the technique was similar across the trials?

DR. WU: Of course there are some iterative design changes, but there's no fundamental changes. And the technology remains the same. There's another term. It's a trademark for a particular device called EECP, enhanced external counter-pulsating devices. As far as I know, the technology mainly remains the same.

DR. BARON: The major difference that I could see in the literature was really -- was how long it took to complete the course of ECP. So it's standardly supposed to be 35 hours, an hour session at a time, over 7 to 8 weeks. Some of the studies did compress that into 4 weeks doing two sessions a day for some of the patients. But, in general, the amount of pressure that they applied with the device was about the same, at least in the RCTs. There was such a wide breadth of observational studies, I can't

say for sure if it was the same across all of those.

DR. KANDZARI: Thank you.

DR. YANCY: We still have several minutes. So let me make certain that others on the Panel with expertise in coronary revascularization have at least had an opportunity to speak. Either Dr. Dehmer or Dr. Hirshfeld, do you have questions or concerns about anything you've heard?

DR. DEHMER: No, I do not.

DR. YANCY: Dr. Hirshfeld?

DR. HIRSHFELD: I just have one question for Dr. Baron. When you plumb all the depths of the scientific data about this technique, it seems to me that there are two objective measurements as opposed to subjective endpoints that exist. The one is the time to ST segment depression on the treadmill. And the other is the coronary collateral flow index. Everything else is subjective. And there's reason to believe that some of this may have been training effect since there was demonstration that patients exercised longer but had the same peak VO_2. And then there was evidence that in the sham group, that there was an increase in exercise duration that was not statistically different from the others.

So how do you put this all together in terms of the actual magnitude of this beneficial effect of this treatment?

DR. BARON: So I'm an interventionalist by trade --

DR. HIRSHFELD: So am I.

(Laughter.)

DR. BARON: I love stents -- no. I share the same concerns that you raise as well, that I think that there's a huge possibility for subjective changes in what people report, in reporting chest pain. And I agree with you that the actual objective evidence of change in exercise duration was possibly placebo at that point. The change to ST segment depression was significant, but it was a small trial. One of the other RCTs, which looked at 42 patients, was primarily looking at physiological changes, did do a couple of secondary endpoints to look at exercise duration as well. Again, 42 patients, very small, not powered for anything. They did also find an increase in exercise duration in the ECP-treated group.

I think there's a signal to suggest there may be a possible benefit to ECP, but I don't think it's as strong as anything that we use currently in our armamentarium, such as PCI, nitrates, ranolazine, et cetera. So I think for patients who have no other option, who we've tried everything for, I think that there's a role for this, but I don't think we should use it in place of something else that we've already -- that we know it works because I don't think the data is there to say that this is 100% definitive.

DR. YANCY: So, John, I guess one way to put this in context or perspective would be to look at the incremental gain from ranolazine when added to conventional therapy versus ECP and determine if you believe it is

in that same realm.

We have two surgeons --

DR. ZUCKERMAN: Dr. Yancy, sure, could -- this is a really important point that Dr. Hirshfeld brings up. So, Dr. Baron, in summary, you would stand behind your slide 53?

DR. BARON: Absolutely.

DR. ZUCKERMAN: And I would ask the Panel members to look at that carefully because I think this puts it into perspective.

DR. BARON: Absolutely.

DR. YANCY: Thank you, Dr. Zuckerman.

We have two surgeons who deal with this on a regular basis, and I'd like to give them an opportunity. So Dr. Katz and Dr. Doty, do you have any questions about anything you've heard from FDA this morning?

DR. DOTY: I just have one question about the possible health risks. You mentioned in the MDRs there may be injury to the skin or those types of issues with these devices, particularly in patients that have peripheral arterial disease or chronic stasis ulcers, longstanding effects of diabetes. Could you comment a little bit more about those, what you found in your review?

DR. BARON: So in the randomized controlled trials, they didn't really go into detail on exactly what skin abrasions was, although it was noted that when folks wore a protective stocking underneath the ECP

device cuffs, that those were diminished, the effect of the skin abrasions were diminished.

As far as people who had extensive peripheral arterial disease, I don't know how many of those patients were included in the RCTs. There was a case study -- case series of over about 20 years of patients from Pennsylvania. It was a single study center that was looking at the effects of ECP in patients -- in treating patients with claudication and rest ischemia. It was primarily observational; it was descriptive analyses that suggested that there might be a benefit, but it was an unpublished descriptive analysis. They did not report any particular adverse events using it in that production, but again, this is an unpublished, descriptive report. So as far as in the published literature, there wasn't a whole lot about it.

DR. YANCY: Dr. Katz, any questions?

DR. KATZ: Just my general concern would be that, depending on the patient's heart rate, that this device could actually end up increasing afterload in patients who require a decrease in their afterload; and as was just raised, just concern about the actual physiology of the quoted long-term benefits. But I think they've been addressed.

DR. YANCY: Yeah, the long-term benefits are of curiosity.

Dr. Brinker and Dr. Slotwiner, do you think this issue of electrical activity generating arrhythmias is plausible, or it's just the natural history of the disease that patients have? But, in addition, Jeff, I know you

have a question.

DR. BRINKER: Right. I'd like to speak on my question first since -- thought of your question. We're looking at a whole -- a number of devices in general here. And I'd like to just be sure that they're harmonized with regard to indications, that all of them available now have basically the same indications, labeling. And whether either in the labeling they have now or in the advertisements advertising that they do -- do they -- is there any -- aside from these somewhat poor publications looking at indications outside of chronic angina, are there any indications in the labeling or advertisements suggesting these other uses?

DR. WU: The cleared indications for those 510(k)s are highly inconsistent from one to the other. And, some of them only include peripheral vascular indications. Some of them included only musculoskeletal. But the majority of them include the cardiac indications I listed previously.

DR. BRINKER: So all those, including cardiogenic shock and --

DR. WU: No. Just --

DR. BRINKER: No?

DR. WU: Like I said, I think -- I don't remember the exact numbers, but a very small number of the 510(k)s do not include any of those cardiac indications.

DR. ZUCKERMAN: So Dr. Brinker, I think your point is well

taken. Regardless of the input from the Panel today, the Agency needs to review the labeling for these devices and appropriately label these devices. Is that where you're going?

DR. BRINKER: Yeah. And I wanted to know whether part of the drive to split this was based on indications that aren't now indications, but I'm getting the feeling that they're so nebulous now that they could be considered indications and they could be advertised for, so that needs to be fixed.

The other piece of this is -- I think Dr. Katz was alluding to in one case, and that is contraindications. Are there harmonization into -- related to contraindications such as a plateau heart rate above which one is unlikely to get any benefit and possibly some harm. So are there the same exclusions and inclusions and, you know, relative contraindications?

DR. WU: The contraindications listed in the labeling by different manufacturers are highly inconsistent as well. And just sometimes the contraindication in one labeling is actually the indication in another 510(k), so it's highly inconsistent.

DR. BRINKER: So one of the issues that I have is that since we're dealing -- we're discussing whether to move these two, let's say a Class II, even for the indications that -- the one indication that I think we probably could all agree on, the other pieces that might not be addressed are differences, for instance, in exclusion or inclusion based on physical

attributes, excessive body weight, heart rate, heart rhythm. So it would seem that this wasn't looked at really carefully for their initial approval, 510(k) approval. And if it wasn't, maybe it should be on the occasion of this thought of reclassification.

DR. BARON: And so in response to that, the randomized trial, the MUST-EECP actually did exclude -- they excluded a lot of people. I didn't go into all their exclusion criteria, but people who had frequent PVCs such that they didn't think the device could track, afib people were excluded, people who had blood pressure over 180 because they didn't want to increase their blood pressure. So there were actually a fair amount of exclusion criteria for that trial. So I agree with you that it would be important to include that.

DR. BRINKER: Yeah, and harmonize the labeling. I assume that the trials like this are probably with a single manufacturer, and so it might not be across the board.

And as far as your question about arrhythmia, I think the anxiety of -- and sometimes there have been some discomfort with the inflation and deflation -- might cause some minor arrhythmias, PACs, PVCs, atrial fibrillation in patients who were borderline compensated in the beginning. But I don't think any significant arrhythmia outside of leakage of electrical current would be, in all likelihood, due to this.

DR. YANCY: Let me just press Dr. Brinker's question in a very

specific way. Of the several devices, five that are on the market, do all either -- or any have an indication for heart failure or vascular at present?

DR. WU: Yes.

DR. YANCY: That's probably something --

DR. WU: Actually, the first congestive heart failure indication was cleared in 2002. For other cardiac indications, cardiogenic shock, acute myocardial infarction, angina were cleared back in the 1980s and in 1990s.

DR. YANCY: So that's interesting, because the PEECH trial was published in 2006. And so there was a heart failure indication in 2002. So that is something that we should continue.

Dr. Greenfield, did you have any questions about the peripheral vascular disease indication?

DR. GREENFIELD: I just wonder in view of some of the confusion or mystery about the worst adverse events whether you were recommending any postmarketing surveillance for any of these situations?

DR. WU: So we have not thought about that because the only reason is, the overall adverse events is low, 54 events over 13 years, and according to industry estimate, about 18,000 to 20,000 coronary artery disease patients are being treated annually in the United States. Maybe we can follow up with our epi colleagues to look into this a little bit further.

DR. GREENFIELD: But where the indications are questioned now, would you have any concern about their use in those areas?

DR. WU: Do you mean the -- the Class II indication we are proposing or for all the indications we have cleared?

DR. GREENFIELD: Where you have cleared some indications that are questionable now, are questions are being raised, I wonder, whether you have sufficient concern to recommend some additional reporting.

MR. AGUEL: Hi, Fernando Aguel. I am Acting Senior Reviewer and Team Leader for the Circulatory Support Devices Branch.

I think what we're focusing on at this meeting is looking at all of the indications that FDA has cleared and getting a recommendation for which ones should be down-classified to Class II with special controls and which ones should remain Class III. And, eventually, those that remain Class III, there would be, as Marjorie Shulman mentioned earlier, there would be a call for PMAs, where data would have to be provided for reasonable assurance of safety and effectiveness to support that specific indication.

DR. YANCY: And that could obviously prompt a postmarket surveillance program.

MR. AGUEL: That's right.

DR. YANCY: We have time for one more question. Dr. Cigarroa?

DR. CIGARROA: This is more a comment than a question getting back to a discussion regarding what is the value of a therapy or

medication on top of standard anti-ischemic therapy. Ranolazine increases exercise duration by about 34 seconds, improves time to ST segment depression, defined by 1 mm or greater, by 30 seconds, and improves the worsening angina from 8% down to 5%, so just as a perspective relative to what we're seeing presented here today.

DR. YANCY: That's helpful information.

I'd like to again thank the FDA panel, Dr. Wu, Dr. Baron, and Dr. Tazar [sic]. You've provided us really excellent information. So the Chair and the Panel really appreciates that input.

We now will proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel and to present data, information, or views relevant to the meeting agenda.

Ms. Waterhouse, our Designated Federal Officer, will now read the Open Public Hearing disclosure process statement.

MS. WATERHOUSE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you have with any company or group that may

be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. YANCY: There has been a request to speak by the following: That would be Diane Zuckerman, Ph.D., President, National Research Center for Women and Families. I see Dr. Zuckerman is here. Thank you. You will be given 5 minutes to address the Panel. Once you have begun your comments, we would appreciate it if you would state your name again, your company that you represent, and any affiliation you may have with entities presented today in the context of the statement that Ms. Waterhouse just read.

Hit the button, please, at the base of the microphone.

MS. FRANCE DE BRAVO: I'm actually presenting -- it's in lieu of Diana Zuckerman. I also work at the National Research Center for Women and Families.

My name is Brandel France de Bravo, and I'm pleased to have the opportunity to speak today on behalf of the National Research Center for Women and Families.

Our center does not accept funding from device companies, and I have no conflict of interest.

Our nonprofit center analyzes and reviews research on medical issues and provides objective and understandable information to patients and providers. Also, we are an active member of the Alliance for a Stronger FDA, a nonprofit coalition of corporations and nonprofit organizations that has successfully increased resources for the FDA by billions of dollars.

I have a master's in public health from Columbia University, and I've been working on health and safety issues for over 20 years.

After reviewing the safety and efficacy data on external counter-pulsating, or ECP, devices, we have concerns about the FDA's recommendation to split the classification, down-classifying one limited indication to Class II with special controls and requiring all other uses to be cleared through the Class III PMA process.

We agree that the research supporting the use of EC devices for refractory chronic stable angina is convincing. It's nice to know that something that's been on the market and been used by at least 18,000 people with coronary artery disease a year for 13 years or more actually helped some of them. And there is no evidence of substantial harm.

We were disheartened, however, to see how little research had been done or even collected and presented to the FDA by

manufacturers on the efficacy of ECP devices for the many, many other cleared uses, ranging from cardiogenic shock to necrotizing cellulitis. The wide array of unsubstantiated cleared uses underlines the potential for the misuse of the medical device once it is on the market.

Now, the FDA synthesis reported only one recall, which was a Class II moderate risk, but we did find a second Class II recall by checking the product life cycle. I think they both were in 2009. The recall described an FDA synthesis-involved customer complaints and software errors. Now, assuming that no patients were physically harmed by recalled ECPs, continuing use of devices with no demonstrated efficacy contribute to the high cost of healthcare, and let's face it, that does harm everyone.

While the safety profile of the device thus far, and I emphasize thus far, appears acceptable, we have reservations about the FDA's proposal to split the classification regulation. A split can easily become a loophole. Devices can legally be used off-label. Unfortunately, this week's court decision, *United States v. Caronia*, says that companies have the right to promote their products for off-label uses. That would certainly be harmful for patients and would be reason enough to keep this product as a Class III device for all uses.

Secondly, even though the ECPs have been useful for refractory chronic stable angina, there's no guarantee that future modifications to ECPs for that purpose will be as safe or effective as the ones

currently on the market.

Without the safeguards of the PMA process, there's simply no way to know if new ECPs would be as good as the ones currently available. Clinical trials are needed, not just lab tests, to make sure that the new products are safe and effective.

As all of us know from the Institute of Medicine's report, where they stated the 510(k) does not require evidence of safety or efficacy, so all of us know that this is a huge issue for these devices.

In conclusion, we do not support the FDA's recommendation to down-classify ECPs for refractory chronic stable angina. We would support allowing the ECPs that are currently on the market to be allowed to stay on the market with labeling to include the phrase "all 510(k)-cleared ECPs are prohibited from being used for any indication other than refractory chronic stable angina."

We urge you to require all new versions of ECPs to be classified as Class III and go through the more rigorous PMA process for any uses.

Again, thank you very much for hearing me out. My name is Brandel France de Bravo, National Research Center for Women and Families. Thank you.

DR. YANCY: Thank you very much.

We don't have any other speakers that are registered to speak

during this open hearing. I will pause for a moment and see if there is someone who would wish to address the Panel.

(No response.)

DR. YANCY: Seeing no person approach other than the speaker that we've already had, I would go to the Panel now and request that you raise any questions you might have for the single speaker we've heard during the Open Public Hearing.

Dr. Slotwiner?

DR. SLOTWINER: Thank you. I just have a question maybe for Dr. Zuckerman. Is there a precedent for a label prohibiting use of a device for off-label use?

DR. ZUCKERMAN: Not that I can think of. That's not the way we generally label devices. But I do think that when we go to the actual question section of this Panel meeting, we heard loud and clear from several Panel members the importance of appropriate labeling. And labeling is a special control, and we can delve into that further.

DR. YANCY: Thank you.

Dr. Brinker?

DR. BRINKER: A somewhat compromised approach might be to -- as I understand it now, if we split, then the companies would have a year or so to arrange PMA trials for indications that are not, let's say, chronic stable angina. And I also understand that they would be continuing to sell

their devices and under the current labeling for them -- is that not true -- in that period pending the clinical data?

DR. ZUCKERMAN: Yes. We don't want to put the cart before the horse and, really, we're looking for independent advisory panel input from really a great collection of people today.

But I think you've raised some important general points. Number one, if there are appropriate indications for Class II, then we want to hear from you. But if you do believe that indications are more appropriate for Class III, then hopefully, this Advisory Panel will help incentivize the industry just to do it, just like that Nike commercial, we need to do it.

(Laughter.)

DR. ZUCKERMAN: In the interim, though, we are very aware that if there's true intent on the part of an industry to do appropriate trials, we're going to allow that to take place rather than just remove devices that are potentially helpful from the market. So in spirit, I would agree with you, Dr. Brinker.

DR. BRINKER: So if they wanted to -- so my argument, which is sort of addressing the last speaker's issue, is that if we said that only -- for indications not chronic angina, the only way that one could do them was in a clinical trial. And I assume that these have to be done under an IDE, all these premarket clinical trials, or would that not be a situation here?

DR. ZUCKERMAN: No, I think in general, you're on the same wavelength with our prior speaker in that, number one, you would like the Agency to appropriately review labeling so that this class of devices is more appropriately labeled, and then for new indications, we would be obliged with the industry to use our standard paradigm, which would be an IDE trial, hopefully resulting in a PMA.

DR. YANCY: When we get to Question 4, I think we have considerable latitude to discuss this further, Jeffrey. So thank you very much.

Dr. Lange?

DR. LANGE: I just wanted some clarification of what the position is of the center you represent. And so if I understand, what you mentioned is that the major concern about this particular device, not harm to the patient, but overuse, which harms society in general, and that the major concern about reclassifying it from Class III to Class II is that it may be overused, and that would be the harm. So is the center's position that there should be no Class II devices, any of them -- yes, I'm going to ask you to respond -- because any of them could be overused? Is that the position of the center?

MS. FRANCE DE BRAVO: The position of the center --

DR. YANCY: For the purposes of transcription, you'll need to restate your name, please.

MS. FRANCE DE BRAVO: Absolutely. It's Brandel France de Bravo, National Research Center for Women and Families. In general, the position is -- I hate to say in general. But okay, the difficulty with down-classifying these kinds of 510(k)s are that new iterations may not be as safe and effective. So we're just opening the door for potentially ineffective or harmful devices down the road. So there's, you know, indication creep. That can happen even with a PMA-approved device, but at least there's a more substantial body of clinical evidence that sort of fences that creep in a little bit, whereas with a 510(k), the boundary is not very well-defined, and so it's very easy to promote off-label uses. But separately from that, there is also this issue of just down the road, how do we know that new ECPs will be as safe and effective. I mean --

DR. YANCY: I think, though, what I heard you say very clearly was having dissimilar classifications creates a loophole.

MS. FRANCE DE BRAVO: Yes, that is exactly what I'm saying. Thank you, sir.

DR. LANGE: So, again, let me ask the question simply. Does the center represent that there should not be any Class II devices?

MS. FRANCE DE BRAVO: Oh, no, I don't think we would ever say that. Of course not.

DR. LANGE: Okay.

MS. FRANCE DE BRAVO: But we're talking about devices that

are -- I don't know how to call it -- whether they're grandfathered -- these pre-'76 devices that have been sort of allowed to move along and move along with 510(k), which substantial equivalency, if one isn't careful, it can become a bit of a house of cards because a device is being compared to something that's being compared to something; none of those previous devices have clinical data. They may have lab testing. They may have all other kinds of testing, but it's not the same thing particularly if it were implanted, which this isn't, but we have that even with an implanted device like hip replacements. Does that -- thank you.

DR. YANCY: Additional Panel questions? Dr. Allen?

DR. ALLEN: This is probably a question for Dr. Zuckerman to answer. You know, as a Panelist, I am very concerned about approving something with a specific labeling and then having that device, particularly if it's very invasive and very expensive, disseminated to the public in an off-label fashion. Perhaps the Agency could give some clarity on inter-governmental discussion between sister agencies, specifically CMS, with regard to how you're going to move forward with labeling use tied to reimbursement because that -- to me, the precedent was set with percutaneous valves, I think, appropriately so. But clarity on that issue to the Panelists may help when they're making these crucial voting decisions.

DR. ZUCKERMAN: Certainly, we talk with our CMS colleagues, and Dr. Allen, I think this is a good example where we need to talk with our

CMS colleagues on what the results are of this Advisory Panel and what our subsequent recommendations are. But CMS does have a different mandate, and they do operate independently of us. However, they are very cognizant of the fact that our recommendations can impact on their subsequent policies and, you know, this can be easily done.

DR. YANCY: Before we take a break, let me request any comments from Dr. Naftel based on anything we've heard today, particularly with regards to the integrity of the data we've seen.

DR. NAFTEL: It's always fun watching good analyses of data. It just feels good.

I had a couple questions when we get to the details. On the MDRs -- so there were 54 that are reported, so I had a question how many of those were user or facility, and how many came from industry, because it's always interesting to see if they match up.

And it's also very interesting that the last MDR was in 2007. There haven't been any since then. So that's of great interest.

Now, immediately, you just can't help yourselves when you see the MDRs, you want to know the denominator, and FDA has given us their best shot, so that helps. So I'm wondering, in that Form 3500A that I can see in my mind, the MDR form, could you imagine a check box that says, "Was this device used off label?" Would that be just huge? And it would start to get at some of what we're trying to learn. And then go back to

industry and say, "You give us your best denominator count of how often it's used." And then we would really start to learn something. The MDRs, which are incredibly valuable, would become more valuable. We could see, does the rate of these events increase with off-label use.

Now, of course, you know, the companies might resist that a little bit, but it would sure be fun to add that box or the FDA to just look at the text box. And because these are all short-term events and we're not looking at long-term, it makes it easier. I bet you could look at the individual form and get a feel was this for chronic angina or not.

So just random thoughts.

DR. YANCY: So what I'd like to request, then, is when we reconvene after the break, if FDA could specifically address those questions, that would be helpful.

Dr. Zuckerman?

DR. ZUCKERMAN: Okay. Perhaps the other Panel members want to talk, and then I'd like to make a general comment about Dr. Naftel's comment.

DR. YANCY: Are there other Panel members, then, that have a question?

Dr. Hirshfeld?

DR. HIRSHFELD: Yeah, I'd like to go back to Ms. France de Bravo. So I'm trying to think about the implications of what you're

advocating. So what your organization advocates is not down-classifying this device to Class II even for one indication, leaving it as a Class III device. So the potential implications of that would be that that would trigger a requirement for an appropriate clinical trial to demonstrate efficacy in the indication that we've discussed. And so the implications of that might be that those clinical trials, given that we've already seen that the detected benefit is modest, those clinical trials might fail. And that, I imagine, could potentially have the impact of withdrawing its approval and withdrawing the device from the market. Is this something that you're considering would be an appropriate consequence of the position you're advocating?

MS. FRANCE DE BRAVO: I recognize that in this economy, we don't like to talk about anything like that, but on the other hand, again, in the context of this economy and spiraling healthcare costs, I would say a device that has not been proven effective, even if it's safe, should not necessarily stay on the market. I don't know. Is that -- that may seem revolutionary -- I don't -- or maybe that's comparative effectiveness. And I know that's not the role of the FDA obviously, but yes, I think you are correct. Again, Brandel France de Bravo. Thank you.

DR. YANCY: I'd like to call this Open Public Hearing to an end, and we will end with Dr. Zuckerman's comment.

DR. ZUCKERMAN: Okay. Dr. Allen, you still have your light on -- did you -- okay. So if I were to summarize the last set of questions by

Panel members so that the FDA can appropriately respond when we come back from break, I think there's a uneasiness about potential off-label use, A, and B, there's a question about what is the real adverse event rate when used in the real world.

Now, interestingly, even in Class II as a special control, we can employ postmarket surveillance, and perhaps after the break, we can spend a few minutes talking about that. We're privileged in that Ms. Christy Foreman, our Office Director here at the Center for Devices, is in the audience, and she can help the Panel on this important topic with a few comments.

Thank you.

DR. YANCY: Thank you, Dr. Zuckerman. We'll take a 15-minute break and reconvene at 10:15. We are 30 minutes ahead of schedule, so I hope we can continue this path.

Thank you.

(Off the record at 10:03 a.m.)

(On the record at 10:20 a.m.)

DR. YANCY: -- and questions about the different attributes of the MAUDE database and MDR reporting and the possibility of being able to identify uses of devices that were consistent with labeling and not consistent with labeling. And then important questions were raised regarding FDA protocol with regards to indicating that certain applications for a device

were appropriate and others would be specifically highlighted as being inappropriate in an attempt to referee or govern the use of devices approved through the 510(k) process for indications for which there are remaining questions about data and effectiveness and/or safety.

Dr. Zuckerman has identified an FDA officer who will take this discussion further. If you'd proceed, please, and please identify yourself at the time and for your comments.

MS. FOREMAN: Good morning, everybody. My name is Christy Foreman. I'm the Director of the Office of Device Evaluation. So I'll try and provide some clarity to the questions that were asked.

First, describing the plan that we are talking about here. Our proposal is to take what you saw is a myriad of indications and say that we have found sufficient evidence for the angina indication. So we are proposing that for those refractory patients, there is some potential benefit, and we don't see outstanding safety concerns that cannot be mitigated through the application of special controls. So we are proposing the Class II indication for angina.

For all other indications, we have not found sufficient evidence to support benefit, so we are proposing that those indications be Class III indications requiring a PMA. That would be consistent with my understanding of the CMS coverage decision, where right now CMS is only covering for the angina indication. They are not currently covering the other

indications. So that may address the off-label concern.

And there was a question about postmarket surveillance. So with respect to postmarket surveillance, the special control authority given to us in the statute identifies postmarket surveillance as a potential special control. If we were to apply postmarket surveillance, that would apply to every manufacturer who wanted to market the device. While we have that authority, we have not explicitly invoked postmarket surveillance as a special control currently, but we could do it. But what that would mean is that every manufacturer marketing a device would have to come with a postmarket surveillance plan.

Given the number of MDRs that we've seen, it is relatively low, and given the fact that we were proposing to limit the indication set for which we saw some potential benefit, we did not include a plan for postmarket surveillance. The MDR provisions, the Medical Device Reporting provisions, applies equally to 510(k)s and PMAs. So the reporting requirements would not be different based on the classification.

And then there was also a question about the process and whether IDEs would be needed. So to clarify, we are a government agency. We do have what some might call bureaucratic processes. So the first step in the process was the 515(i) order that was alluded to, where we asked for the available safety and effectiveness information. We have reviewed that information. We are now here at Panel today to seek your input into this

process.

After this meeting, we will factor in your decisions today into our processes. We will then issue what's called a proposed order. The proposed order would identify the Agency plan. That order has a notice for comment, opportunity for comment. We would review the comments we receive, and then we would finalize that order. Once we finalize that order, manufacturers would have 90 days to submit PMAs for those indications they would continue to market the devices for, other than the Class II indications. For the Class II indications, there is no action required from the manufacturer. It's only those Class III indications that we would require a PMA.

So there is some time in the process by which the manufacturers could gather data if they chose to take the Panel's recommendations and gather that data today. Since those indications -- if the manufacturer already has that indication on their label, they would not need an IDE to gather data for that indication. Once we call for PMAs, however, an IDE would be needed because we would say you need a PMA, and we would consider the device as adulterated and misbranded without that marketing application or an exemption under the IDE provisions to allow study.

So I'll pause here and see if there are any questions from the Panel on that.

DR. YANCY: So to be clear, if we determine that the indication for any device, several being discussed in the next two days, merits a continued classification as a III, that is reconfirmation as a III but it needs to go forward for PMA, then for that indication, the device would need an IDE, and there would be some time allotted for the sponsor to make application for PMA; is that correct?

MS. FOREMAN: That is correct. And we say that an IDE would be needed at the time that we call for the PMAs, when we finalize that order. That is when the IDE would need to be in effect. For some of the devices that we're talking about today, the firms may actually have data. So just because we call for PMAs does not mean that each and every firm would have to conduct a prospective study. If they already have data demonstrating reasonable assurance of safety and effectiveness for any of the devices under consideration, they can submit that as part of their PMA without the need to actually collect any more information. The difference is other firms cannot leverage that information. And that's what the 510(k) system is really predicated on, is leveraging a body of knowledge, that if it applies to one device, it applies to all devices, whereas the PMA program is an independent assessment of safety and effectiveness.

DR. YANCY: And so if I can just press one more question. The time allotted, let's call it a grace period, does it have a finite boundary? That is, is it X number of months to respond to submission of the application,

then X number of months to have data amassed to go forward with the PMA?

MS. FOREMAN: So we have handled some of these on a case-by-case basis. Generally speaking, when we issue the final order -- so we would issue a proposal signaling the Agency's intent. There is a comment period, and then the Agency considers the comments received, and then we would have to prepare a final order. So that can be up to a year or so in between the issue of the proposed and the final, or in some cases, we're here today because it can be even longer than a year.

(Laughter.)

MS. FOREMAN: We're trying not to extend those time periods, though. But once we issue the final, if we do not make any exceptions or consider an extension, it would be 90 days from when we issue the final order that we would have to receive a PMA in-house for the firm to continue marketing that application. If there are extenuating circumstances, we may consider granting an extension. We would have to consider that on a case-by-case basis, and we would look at the public health impact of doing that because our intent is not to deprive the clinical community of devices that are already out there. Our intent is just to make sure we have the appropriate regulatory scheme in place for the continued regulation of these products and that we do gather the data that we need for certain indications.

DR. YANCY: Certainly, if de novo data collection needed to take place, which would necessitate design of a clinical evaluation experience, or trial, if you will, follow-up, and then analysis, that clearly could take several years, possibly?

MS. FOREMAN: It could.

DR. YANCY: Questions from the Panel for the FDA in these specific areas. Dr. Slotwiner?

DR. SLOTWINER: I just wanted to ask you to clarify if you could, you mentioned if it is a Class II special controls, we could use the postmarket approval -- or postmarket surveillance might not be practical. But did you mention something else before at first that you could use --

MS. FOREMAN: So postmarket surveillance could be an applied special control, and it would apply to all firms. If we say that a special control is postmarket surveillance, any firm who markets the device would have to have a postmarket surveillance plan. So we would have to capture information about the actual uses, the adverse events, we would have to craft that plan, what would the surveillance plan look like.

What I mentioned also was the MDRs, the Medical Device Reports, and I said that the MDR requirements apply equally to 510(k) devices and PMA devices; there would be no difference in the reporting requirements, depending on the classification.

DR. SLOTWINER: So the surveillance could be a tool to prevent

over-utilization under non-indicated usages, or not really?

MS. FOREMAN: So it's probably not the best use of that program. We would collect the data related to the use of it. The FDA does not regulate the practice of medicine. It has been our position that we regulate manufacturers, and we regulate what a manufacturer can say about a medical device, that they have to have -- there are certain requirements, and if they don't meet those requirements and they're promoting for a new intended use, we have said that the product is adulterated and misbranded. Obviously, with recent court cases, we will have to assess that and see how that -- that case that was mentioned applies to drugs and a pharmaceutical rep. We would have to see how that would apply to medical device regulations.

But it's our provision that we regulate the manufacturer. So a manufacturer could not promote the device for off-label use. But we don't actually regulate you as a physician and what you choose to do in the best interest of the patient.

DR. YANCY: So several comments have come up. So I've seen Dr. Brinker, Dr. Yuh, Dr. Allen, and Dr. Hirshfeld.

DR. BRINKER: So I just want to make sure because I thought I heard potentially two different things. If we split this and say that there needs to be a PMA, let's say, for acute coronary syndrome, acute myocardial infarction, peripheral vascular disease, and heart failure as the separate

indications, and we've already said that that will need to be supported unless they have tons of data that's unpublished. And I assume that if they present that to you, would that not have to go through a panel, or would it have to go through a panel?

MS. FOREMAN: So our requirements for taking a device to panel is if it is a first-of-a-kind and the manufacturer wants us to take that indication to panel, we are obligated to bring it before the advisory committee. If it is not what we consider first-of-a-kind, we are not obligated to take it to an advisory committee. So we would then look at the data and rest on the merits of the data. If the data is a clear-cut case of supporting safety and effectiveness, we might not need to come before the advisory committee. If the data is questionable, we may actually bring the data here to seek your input as to how to interpret the data in terms of the appropriate labeling and patient population.

DR. BRINKER: Okay. So that's okay. Now, the other piece is, in the interim period, let's say that they don't have this ton of data that they're going to present to you -- or even if they do, and you don't have it, and it takes you six months to work on it -- but let's just say that they're going to do an IDE. And if it's done in less than a year-and-a-half, it'd be a miracle, that is, a clinical trial. But during that time, I'm still not clear on whether they could still advertise and label what they have now, which we would find unfounded as of yet. And I think the answer to that is yes, and

I'm not overwhelmingly happy with that.

MS. FOREMAN: So that's a great question. Until such time that we call for PMAs through the final order, the firms are allowed to market the devices for the indications they've been granted through the 510(k) program. When we call for -- if we were to implement the strategy as proposed, there would be no -- the only thing the devices would have to do to remain on the market is to change their labeling to be consistent with the refractory angina indication.

For the PMA indications, once we issue that final order, they would not be able to advertise the devices for that use. They could, however, have an IDE that would allow continued access. The IDE can get reimbursed from CMS, so that would be a way under the -- it would be my understanding that if they were to do the study, they already have the indication now, CMS is not reimbursing for those indications is my understanding. You probably would not get reimbursement for uses -- or if you did a study before we called for PMAs and you did not have an IDE.

DR. YANCY: Dr. Yuh?

DR. YUH: Yes, thank you. Two questions. One is, in terms of your answer to Dr. Slotwiner's question, basically the postmarket surveillance that would be used as a special control really addresses safety as opposed to indication or efficacy of a device, is that right, as a safeguard for that? Is that a correct assumption?

MS. FOREMAN: Typically, if we're looking at postmarket surveillance, we are not looking at postmarket surveillance as a means of satisfying the safety and efficacy provisions that we would want to see premarket. So, generally, it would be an ongoing surveillance to make sure the safety profile of the device does not change.

DR. YUH: Understood. And the second is, just out of curiosity, is firm data admissible in reclassification deliberations?

MS. FOREMAN: Yes, it is.

DR. YUH: It is? So if a company felt that they wanted to push for a reclassification of a Class III indication, they could come forward with data in support of that?

MS. FOREMAN: Yes, they could.

DR. YUH: Okay.

DR. YANCY: Dr. Allen?

DR. ALLEN: I think she answered my question a second time in that I just wanted clarity on the fact that CMS currently has an NCD that confines reimbursement to chronic stable angina.

MS. FOREMAN: That is my understanding.

DR. YANCY: Just to be clear, that NCD covers only one condition?

MS. FOREMAN: That is my understanding.

DR. ZUCKERMAN: Yes, I believe it was in your Panel pack also

if you want to refer back to it.

DR. YANCY: Thank you.

Dr. Hirshfeld?

DR. HIRSHFELD: Yeah. We've been sort of skirting around the edges of this issue. I'd like to maybe hear some thoughts from the Agency about the balance between safety and effectiveness. Some of the statements say that a device is approvable if the effectiveness and the safety are in an appropriate relationship to each other. So in a situation like this, where we have a device that we're quite convinced is safe, does this mean that we cut it a break in terms of its burden that it has to reach to prove effectiveness, or is there a reciprocal relationship between the estimate of safety and the requirements for effectiveness in order for a device to be approved?

MS. FOREMAN: So that's a great question. We actually just published a guidance document on making risk/benefit determinations. And I think the issue is when you are confronted with a relatively safe device, the magnitude of effect does not necessarily need to be that great. There needs to be a magnitude of effect, so we need to have some data to factor into the equation so that we can say that the benefits outweigh the risks. But if we are dealing with a particularly risky device, we would say that the magnitude must be greater than an inherently safe device because we have to have some reason to tolerate the risk posed from the higher-risk device.

So there's not an exact formula that we use. What we do is we review the data in its totality so that we look at what are the risks that we observed in clinical studies, what are the theoretical risks, understanding that any clinical study as designed will not identify all risks. They're just not sized in device trials appropriately to identify all risks. So some risks are theoretical risks. Usually we address those through bench testing.

So for example, electrical safety. In this case, we mentioned that the original panel identified cardiac arrhythmia as a concern because of leakage current. Well, we have electrical safety testing that we can say that while that's a risk, we can mitigate that risk through electrical safety testing. So we would look at the magnitude of the benefits.

So for these devices, I think what we found is in the refractory angina population, we have found some magnitude of benefit that we can factor in.

DR. HIRSHFELD: Okay. Now, related to that, Ms. France de Bravo highlighted what she might characterize as a societal financial risk of having an approved device out there which is marginally effective, and so she talked about the impact of that. Now, my understanding is that's not our purview. Is that correct?

MS. FOREMAN: So that is not within the Agency's purview. The Agency objective is to identify the appropriate risk/benefit profile for the device and provide accurate labeling. So by providing the accurate

labeling, a clinician or CMS can review the data and determine in CMS' case if they want to make a coverage decision or a physician can determine if they want to use a particular technology over another technology. But it's the Agency's job to make sure that the risk/benefit profile has been established and we can actually approve or clear the product and we can write appropriate labeling.

DR. YANCY: Dr. Allen?

DR. ALLEN: Your publication on risk/benefit, it actually is very good, but I piggyback onto what John's saying in that as a clinician, it's no longer a teeter-totter with risk versus benefit; it's a triangle with risk versus benefit and the cost of achieving that ratio. And I do think that is an incredibly important piece, particularly as we move forward with more expensive technology. And to the benefit of the public speaker, sometimes the most safe procedure that demonstrates a minimal threshold of efficacy unfortunately is exploited and sometimes can be, because it is so safe, can be one of the more expensive ones to utilize.

MS. FOREMAN: I would say the Agency doesn't disagree with that perspective. We, however, are bound to the provisions that Congress has allotted us with implementing, and the financial aspect is not currently part of our decision-making criteria. That would be more within CMS. So we are all one HHS. CMS is part of Health and Human Services. But right now, that piece, that third leg of the stool is not part of our decision-making

criteria, but I do share your concerns.

DR. YANCY: I think this'll be our last question for FDA.

Dr. Greenfield?

DR. GREENFIELD: A new manufacturer comes in with a device that is claimed to be substantially equivalent to the others currently under Class II. What do you require in the way of safety and efficacy?

MS. FOREMAN: So, today, if we were to receive a new application, we would not see any clinical data for that indication. We would rely on the bench testing. We would rely on the labeling to make sure that the intended use is the same; we must first establish it has the same intended use. Then we would look at the technological characteristics and we would have bench testing, validate the technological characteristics compared to a predicate, and that's what we would use to clear a new device for marketing.

DR. YANCY: Thank you very much. We really appreciate the added perspectives that you've provided us.

Let me give the Panel a bit of direction. For the next half hour, we have time allotted for internal deliberations. At the completion of our internal deliberations, at approximately 11, or shortly thereafter, we'll go through some very structured FDA questions for which we need to formulate responses. Let me also remind you that contrary to other panels, we need to resolve this question by noon, because after the lunch period, we have a

second product that we need to review. So we'll have to bring this to closure over the next hour and a half.

I've asked Jamie to once again put up the FDA recommendations so that we can all see the issue that we're addressing. External counter-pulsating was previously approved as a Class III device under 510(k), and it meets the time threshold where it is up for reevaluation. Our choices are either to reconfirm that it is a Class III or reclassify that instead of it being a Class III, it is a Class II device and can continue to be represented on the market with the benefit of a 510(k) approval process. We also have been informed that we can split the classification so that for one indication, the device is allowed to remain on the market with 510(k) approval, in this case, for chronic angina, and for other indications, it would be a Class III device that would then mean we have reconfirmed the original decision of it being a Class III device, but now a requirement for it to go through premarket approval with all of the imaginations therein described by FDA just in the last several minutes.

So I wanted to lay that out. This is our opportunity to internally discuss and deliberate these issues.

Dr. Sonemblak, we'll get to you in just a minute, but I want to be certain that the Panel has given our Patient Representative and our Industry Representatives a time to address any questions that you may have heard this morning.

So, Ms. Gates McCall, if you could start?

MS. McCALL: I have no questions. I have personal experience with this particular device with both of my parents back in the early '80s, so this has all been very clarifying for me.

DR. YANCY: Do you want to share those experiences? You don't have to.

MS. McCALL: Well, all right. Understand that my maternal side of the family is 5 feet by 5 feet, so all the cardiologists in here went, oh, yay. We used this particular device on my mother after her second MI. It was recommended by her surgeon, actually. Unfortunately, it was not successful because the bands didn't fit; she was 5 feet by 5 feet. Now, 15 years later, it was used with my father after his CABG, and it was extremely successful. He actually had unstable angina prior to the CABG. The CABG was successful. But also, in the process of the 35 hours that he had, he experienced no more angina after that. So I've had a neutral experience with this as well as a positive experience with it.

DR. YANCY: Thank you very much. That actually is helpful.

Mr. Barrett?

MR. BARRETT: Thank you. No one from this industry has approached me prior to this meeting with any comments or feedback. So I'll just say that from my own point of view, I felt the Agency's clinical presentations this morning were very clear and thorough, and that with my

understanding of the regulatory scheme, that the Agency's proposal is quite reasonable.

DR. YANCY: Thank you, Burke. I appreciate your input.

I want to begin our deliberations. And, again, I'll go to Dr. Sonemblak, but my opening perspective is just one of a theme that Dr. Naftel introduced, that is, thinking about denominators here. 20,000 uses per year seems like a considerable number of uses, but for a disease that impacts maybe as many as 12 million people in this country, we're somewhere in the magnitude of less than 1% of the people with the disease are being exposed to this. So I think that the scale of use is as important for us to consider, and then again, the number of events at least reported as being adverse is really quite sparse, almost nil. Clearly, we have questions about efficacy even for the one indication where there appears to be clarity. And from my view, what we see for heart failure and peripheral vascular disease is really something that needs further discussion.

So let's begin with Dr. Sonemblak. Thank you.

DR. SOMBERG: Well, angina is a very complex syndrome to treat and develop drugs and devices for. With that said, I just wanted to give you my perspective because I was involved in, oh, the early '80s on in antianginal pharmaceutical trials. And they were difficult, et cetera. In fact, we talked of ranolazine, and that's really the culmination. It's the last, if you will, of the antianginal drugs, and that was on top of fairly homogenized

standard therapy. It's using rigorous protocols to try to avoid a placebo effect, which one sees here, remembering that we're not looking at mortality, but we're looking at quality of life symptom improvement.

And with all that said, the data for the ischemic anginal indication is extremely, extremely weak here. The one somewhat sized -- 139 I think it is -- patients is very small. There were 700 in the pivotal trials for ranolazine plus patients. It's an extremely small number to base the treatment of, you know, tens of thousands of patients even though that is a small fraction of the total number with ischemic heart disease.

But in that trial, we have a negative. It's not blinded, and we have a negative, if you will, primary endpoint, the primary endpoint. So we're dealing with secondary endpoint analyses here.

And while I do agree with the FDA reviewer that there's some signal buried in this data -- I would say it's great hypothesis-generating; it's really interesting that there's a potential mechanism of action even down to the molecular level -- you have to ask yourself, is the data really there in 2012, '13, '14, and on to make use of this.

Besides that, we really have very little information to label. Do we know the dose? That's, in this case, the pressure. Do we know the duration? I mean, it's sort of very arbitrary. Do we know the necessary requisites for re-implementing of that for a durability effect, et cetera?

Now, it's nice that someone after surgery -- unstable angina

has -- that's a more unusual condition -- but has a response as we just heard an anecdotal study. But what's the best way to do that? And would all this really be a placebo effect? And if you've seen this, if you will, treatment in operation, it's quite dramatic. You have someone there with -- on their extremities; they're, if you will, sort of bouncing around, et cetera. There's a tremendous likelihood of impression. When we deal in the pharmacologic therapeutic realm, we're just taking a pill. And you know a placebo pill has a nice effect in angina abatement.

So that's why we need exercise testing. That's why we need to see a prolonged duration of activity. We have to have an ST segment criteria, et cetera, and I just looked through the data and said to myself, you know, this is all anecdotal. I guess if I had a patient who responded to absolutely nothing -- and then again, I'm an arrhythmias guy, so I would give them amiodarone, which has antianginal effects, but if we responded to absolutely nothing and someone came up to me and said, "Give this a try," yeah, it might be an interesting option.

But we're talking here for programmatic/systematic labeling. And I see no reason why we shouldn't ask the manufacturers who have been using this, selling this device for a while, having a lot of experience, to come forward, have a presentation. Sure, we're not going to ask for -- at least I wouldn't ask for a randomized trial of 10,000 patients, et cetera, but we really should have a debate on this and see all the data, whether it's

published or non-published, have critical reviews of it, and maybe even see if we can encourage more data because maybe there's a better way to utilize this. Maybe if you gave it at a higher pressure for a longer duration for multiple interventions, you would have a much more dramatic effect or not.

So I have more questions from this area than I know what to do with, and I think it would be best to request a PMA. Well, I'm not going to go -- recommendations, but I'd like to hear what the rest of the Panel says. But at this point, I'm favoring requesting a PMA-like data or they can ask -- present data and ask for a down-classification, and maybe that is justified.

DR. YANCY: So, Dr. Somberg, thank you for your comments. What I hear you saying is that your vote would be to reconfirm a Class III status for the device for all indications and require premarket approval be the next step.

Let's continue to frame our discussions now around the bigger question of the indication for angina and this notion of reclassification of the device from a III to a II. Are there other comments, particularly those that may be different from the perspective that Dr. Somberg just shared with us?

Dr. Allen?

DR. ALLEN: I share John's concern, but I think you do go back to that teeter-totter of risk versus benefit. And I think John's absolutely correct in that based on this device, if it was presented at a PMA with the

observational studies and the -- even randomized trials, it probably wouldn't pass muster.

I think the conundrum I have is that it appears to be an extremely safe device, and so your threshold for approval within the regulations, not taking into account the cost, you know, you have to balance that.

And so with specific regard to angina reclassification, because it is such a safe device and the efficacy is probably borders on marginal, I think the way it has set it up seems very reasonable. With regard to all other indications, I'm amazed that they've ever been cleared for those other indications because there seems to be very little, if any, data on that that is of any consequence at all.

DR. YANCY: So continuing to frame our conversations around angina, I've asked Dr. Lange to speak about comments that he's previously put in the medical literature about the use of ECP for ischemic heart disease.

DR. LANGE: As the FDA did, having reviewed the data and written about this both in the *New England Journal* and in the ACC education program, I would agree with everything that my colleague has said. In terms of the data, the randomized controlled data being fairly scant, the observational data, although not perfect, if that's a placebo effect, that's a 75 to 80% placebo effect, which is bigger than any placebo effect seen in any trial of any medications.

So, again, I think that the signal is there. It's a weak signal. And the safety is -- none of us are questioning the safety at all. And for those reasons, I think that the FDA's recommendation -- and the FDA, which I think gives very due and a tremendous amount of diligence, and I'm going to say is a hard grader, I think, is probably right in their recommendation to make this go from Class III to Class II only for the indication of angina pectoris. I think the indications for other conditions are scant and not supported by the data.

DR. YANCY: Dr. Cigarroa?

DR. CIGARROA: So, certainly, the observational data is distinctly more robust than the randomized clinical data. In the one small trial that was randomized of 130-something patients, the intention-to-treat analysis focusing on quality of life and reduction of angina showed statistically no difference, and that's what we're talking about here. And it showed no difference in a patient group that had tremendous exclusion criteria. If you had decompensated heart failure, you were not included; if you had an EF of less than 30%, you were not included; if you had indications and were on antithrombotic therapy, you were not included.

And so you know, from my perspective, I think that it is concerning when no randomized clinical trial with an intention-to-treat analysis has demonstrated efficacy.

DR. YANCY: Just to extend your comments, Dr. Cigarroa, given

the timeframe when those data were acquired, that is, significantly predating our use of PCI in patients with coronary disease, one can say that that begs an even greater question, whether or not there is any benefit based on a contemporary approach in the treatment of coronary disease.

DR. CIGARROA: Agreed.

DR. YANCY: Other comments?

DR. KANDZARI: Dr. Yancy?

DR. YANCY: Yes, Dr. Kandzari?

DR. KANDZARI: So I just want to clarify that we should pay particular attention to the FDA's recommendation with regard to the labeling that this is a treatment for chronic stable angina refractory to optimal medical therapy and without options for revascularization.

So in the context of contemporary therapies, whether it be ranolazine or advanced percutaneous revascularization, this would be that particular therapy. And I think it's important for us to think, therefore, in the scale of perspective. As you mentioned, the denominator of 18,000 patients against the context of 10 to 12 million of these individuals, this is really the last option for many instances. I suspect those 20,000 cases are done at a very few, limited numbers of centers, as this has, in many ways, become an obsolete therapy because of contemporary advances in medicine.

And to that end, the guidelines have spoken themselves,

limiting this to as -- or recommending this as a Class IIb therapy. One final comment, though -- so, therefore, I would support this recommendation by FDA with that specific language around not just angina but angina without options.

I would just also maybe ask that you or Dr. Zuckerman just remind us to level-set this discussion, because I think this will permeate the next day-and-a-half of discussions is that although there is a perhaps triangle that we need to -- we think about with the context of cost, that's really not our purview. Our recommendations are based on the evidence and within the regulatory statutes.

DR. YANCY: So I'll take the naïve approach and try to respond, but then I'll defer to the expert. But in my several years of panel deliberations, cost typically has not been a primary driver in our considerations.

Dr. Zuckerman?

DR. ZUCKERMAN: I wonder who the expert is. I would say that you are. I think that we have an asserted mandate that's independent of cost. And Ms. Foreman again reiterated that.

But I'd like to go back to Dr. Kandzari's statement, because these are really last-option patients. And, Dr. Kandzari, in your scheme of treating these patients, you have perhaps TMR in this therapy, and can you help further put your last comments in context?

DR. KANDZARI: Yeah. And I think they're also colored, in part, by our Patient Representative's comments with her own family members. To begin with, the clinical trials, we have no recent trial data since 2009. I think your parents' experience is dated to the 1980s. So it really represents an evolution of treatment paradigm, where now, as you say, the -- at my institution we would really consider patients for very complex either surgical or percutaneous revascularization. But we're otherwise limited to TMR or this therapy. And these have really fallen, in my clinical experience, largely out of favor and supplemented by advances in medical therapy with drugs like ranolazine or advancing beta blocker therapy, nitrates, and other standardized medical treatments.

DR. YANCY: Dr. Somberg?

DR. SOMBERG: I just think we have to --

DR. YANCY: Wait, just one minute. Dr. Allen, can you turn your microphone off? Thank you.

DR. SOMBERG: We have to be very cautious about what the data is because you just discussed that, correctly so, that the labeling is limited for those people who have resistant or -- et cetera. But I'm looking at the trials, and that is a totally different group of people that we look -- to my understanding, the MUST trial had inclusions of essentially people who have angina and exercise positivity.

So you're right that this might be an interesting modality for

patients who have no alternative. But let's study it in those patients and let's make sure we have some indication. I think the sponsors would have a great opportunity here, because there are a substantial number of people who do not have an option for revascularization, who do not want to go through that again and may turn to this as an alternative. But that is 21st century medicine, and they're presenting data from, you know, the -- essentially, based on considerations that were thought of in the mid-20th century. You know, exercise testing was done in the '50s, and that's for just angina patients with no blinding, et cetera, and essentially, this has pretty much no blinding.

I also wanted to just address one thing. You say the placebo effect. The placebo effect can be very major because this is a very demonstrable thing. If you give a pill, you get a 5 or 10% effect. You put someone on this for weeks, and they are having pressure on all their extremities for a period of time, that's quite dramatic. And whether that has some sort of psychological effect or not, I don't know. And there's nothing wrong with having those benefits, too, because it's really a symptomatology effect.

But I just think we're going to squash the potential for new data and new avenues of utility for this process by leaving it or down-classifying it a Class II device, where there will be just either no information, no new approvals, or future approvals would be by the 510(k) process.

DR. YANCY: It is apparent that the language we see before us for the Class II with special controls refers to an indication that is not entirely supported by the available data, and so that is something to be considered.

What I'd like to do is recognize Dr. Ohman and then transition to the non-anginal indications before we begin the FDA questions.

Magnus?

DR. OHMAN: Yeah, so this is interesting. I want to remind everybody, of course, that these trials were not done for gaining approval for the device. So the types of studies that you would carry out for the approval of angina would be, at least in the pharma side of the Agency, would actually require two studies. And we have one here. So that's a little bit unusual in the sense we're resting on one piece of information.

And then if you take the primary endpoint that was selected in this one trial, it is one of the two that the Agency recognized for establishing the effect of a treatment on angina. And, in fact, the other one they recommend, which is time to ST depression, is actually positive in this trial. So, you know, you have to be a little bit careful when you say there's no effect. I don't believe that there is a dramatic effect, but I also don't think the studies were done adequately to address just that particular issue. And we only had one trial, and it's a small trial.

And as far as -- comes to exercise duration, the exercise, time

to ST depression that was shown in this trial is well within the range of all the approved -- ranolazine was brought up earlier -- is actually greater than what was done for PCI. You remember there was a trial way back when where we did an exercise testing study for relief of angina with PCI. Now, that was balloon angioplasty, but that was about the same duration.

So when you take a condition such as angina and you subject it to an objective test, it isn't quite black and white. It's a very shade-of-gray area. You're dealing with training effect. We've already talked about that. I mean, the reality is that this could be placebo, but it could also be training because these patients were trained to exercise more than once to participate in the stress test. And at least, as Clyde would know, in the heart failure, you know, there's actually great literature on establishing the training effect. And none of that was dealt with in these studies.

So I think my bias here is that I think that the Agency has classified this appropriately. I think there is a treatment effect here if you use one of the endpoints that the Agency recommends in general for assessment of this. There is a large safety evidence body here. And I think the other curious thing here, which I don't really -- it's hard to imagine how that would get into placebo -- is the sustained effect.

And if you look at -- remember, this is a 7-week period, but you have treatment effects at least from the registries out to a year. And now that would -- if that's placebo, that's an interesting placebo effect, and

I'm not too sure how I would interpret that.

So my feeling is that this is the right way to do it. There is evidence here. I do not believe going back to a PMA will really solve this.

And just a final sort of word of warning here, which is not quite on topic, but it should be probably known, that there are four or five agents for angina outside United States that are not being brought forward here because the approval process for angina is so difficult.

So we should be aware that this is not an easy field to go into, and we have a device here that offers at least something to patients who are at the end of the rope. And therefore, I think I would be careful how I would add too much more evidence in this juncture.

DR. YANCY: Thank you for those excellent comments, Dr. Ohman.

Let's spend a few minutes going over the non-anginal indications before we go to the discussions.

But, Burke, you had your hand up?

MR. BARRETT: Just a really quick regulatory comment. I think we had good discussion about the standard for drug approval. And just as a reminder, the law, the regulations in this standard, the threshold, if you will, in a drug approval is different than devices. And, in particular, to sort of frame the upcoming conversation, the standard for Class III devices and Class II devices is different. And that was covered this morning, but because

most of the people on the Panel are more accustomed to attending these meetings when we're looking at a PMA for a Class III device, I just want to remind everybody that the threshold for Class II is a reasonable assurance of safety and efficacy. And I don't see that on any one slide anyplace, but I think it's easy to lose that sometimes in the conversation.

DR. YANCY: Point well made.

Any specific comments about use of this device for non-anginal indications, because, again, we will have specific questions about this, and we'll need to formulate answers that will be part of either orders or a plan that the FDA would create. So are there any comments about either heart failure, acute coronary syndromes, cardiogenic shock, peripheral vascular disease, and the assortment of others that were on one of the opening slides?

(No response.)

DR. YANCY: Okay. Well, I'll start and say I think the heart failure information is inadequate and would be very uncomfortable allowing that to remain as a Class III 510(k)-approved indication and would suggest that if there is an intention to represent this for heart failure, that it should remain Class III, reconfirm the Class III status, but it would need to go to premarket approval.

Any discussion about heart failure?

(No response.)

DR. YANCY: Peripheral vascular disease, any discussion about that?

(No response.)

DR. YANCY: Does that no, Magnus, mean that you agree we should treat it like heart failure or you just have nothing to say about it?

(Laughter.)

DR. OHMAN: Well, silence is golden sometimes. But I would say that for all these other indications, and there were a long list of them, we can -- the solidity of the data for angina, but for these other indications, there simply is no information. And while we believe it is safe, in the trials that were actually carried out, so the two PEECH and MUST-EECP, if I remember these names right, peripheral vascular disease, for example, was excluded; heart failure was excluded. And so essentially, in the field, we don't have any randomized trial or any type of evidence to go forward. So I can't imagine that we would say that this is okay under a 510(k) approval process because it simply has to be studied to be evaluated both for safety and efficacy.

DR. YANCY: And as Dr. Baron highlighted and then Dr. Cigarroa further emphasized, the question of risk in the specific setting of heart failure is an important question that needs to be further understood.

Dr. Lange?

DR. LANGE: May I ask a question of the FDA? As Dr. Yancy pointed out, the indication for heart failure was granted in 2002, and how was that or why was that granted? What sort of data was presented?

DR. ZUCKERMAN: Right off the tip of my tongue, Dr. Lange, I can't give you the specifics. We could. But I mean, the general context of this Panel is to say there are lots of indications for this device. Let's take a step back and think of a rational way to move forward. And I think if we could spend our time there, perhaps it would be most -- best used. But we can find out that information. But I think that'll be a general recurring theme for all these devices over the next few days.

What I would like is to continue along Dr. Yancy's line where we look at now that we have the data, are there reasons why we should really take a step back. And we're very fortunate to have specialists at this table. For example, for the peripheral vascular indication, Dr. Greenfield, can you specifically comment on that?

DR. GREENFIELD: I would just say I didn't see any evidence to support that.

DR. ZUCKERMAN: Thank you, as a vascular surgeon --

DR. YANCY: Dr. Lange?

DR. LANGE: Right, let me rephrase my question, Dr. Zuckerman. It wasn't meant to -- the FDA, but say, was there data available in 2002 regarding heart failure that we're not seeing at this Panel, I

guess is my question -- rephrased.

DR. YANCY: You know what, Dr. Lange, I'll actually preempt Dr. Zuckerman and say that the only meaningful database we received is from 2006. So whatever might have been used then, I would deem that by today's standards, we would view it as inconsequential.

But I think from a pragmatic standpoint, we have to acknowledge that for these indications that we vote to remain a Class III, with a requirement for premarket approval, they're likely to go away because the inertia required to generate de novo data especially in a reasonable timeframe probably is not worth the investment of time and resources. And so we should not be operating under a scenario where this is just an operational step. This really is a much more programmatic, almost strategic decision, but -- just so we can get everything on the table.

Dr. Somberg?

DR. SOMBERG: I must disagree with Dr. Ohman here because the MUST trial is with angina. The PEECH trial was with heart failure. The people have less -- the Class II, III heart failure, less than 35% ejection fraction, and you know, it's important to be consistent. In that trial, they met exercise duration criteria, although peak VO_2 didn't change between the two groups. And, you know, once again, I think that could be due to training, et cetera.

And I agree with you, Dr. Yancy, that, you know, I don't think

there's data for ischemic angina, and I don't think there's data for heart failure, and there certainly isn't data for the other indications. But if you think there's enough data in the MUST trial, which is really the most impressive of those trials, for angina, then why not isn't there enough data in your mind for heart failure when you have the PEECH trial, which did meet its primary, primary endpoint?

So I'm just saying is there's such a paucity of data here. Please give thought that maybe there should be an impetus because -- and Dr. Yancy's right. Again, if one indication keeps all these devices on the market and there's no need for clinical data, then they will -- there's no impetus to go for the other indications. But if there's an impetus to get some clinical data, I think that'll be an impetus to go for niches where you can easily demonstrate benefit. And that might be in peripheral vascular, might be in heart failure, or it might be in ischemic heart disease that's unresponsive to medical and procedural therapies.

DR. YANCY: We'll close our discussion within the next several minutes, and so the last two comments from the Panel will be Dr. Hirshfeld followed by Dr. Cigarroa, and then at 11:15, we'll begin the deliberation on FDA questions.

Dr. Hirshfeld?

DR. HIRSHFELD: I just wanted to raise an issue of the role of FDA in regulating the marketing of this product. I happened to just take

advantage of the wifi that's in here, and I looked up www.externalcounterpulsation.com, which bills itself as the official industry site for external counter-pulsation. And on their patient information, they have statements that say it's equivalent to intense exercise, it increases energy and exercise tolerance, it increases alertness and brain function, increases sexual function in men, and reduces the symptoms of Parkinson's disease.

UNIDENTIFIED SPEAKER: Sign me up.

(Laughter.)

DR. YANCY: I wouldn't hardly want Dr. Naftel to comment on the statistical integrity there. So, again, we have to respect our time. Dr. Cigarroa -- but thank you for bringing that to our attention.

DR. CIGARROA: So, again, in terms of what we're being asked, just a reminder, this particular patient subgroup has not been studied. The reported randomized clinical trials did not address this group of patients and did not in an intention-to-treat analysis demonstrate an improvement in angina.

So we are on the slippery slope of extrapolating a patient population that was already in the randomized trial less than 140 patients and making a recommendation potentially to change from Class III to Class II, which I do not support.

DR. YANCY: And to be fair to Dr. Hirshfeld, I think we do need

an FDA response to how marketing will be impacted by decisions that are made or deliberated by this Panel today.

DR. ZUCKERMAN: Well, first of all, Dr. Hirshfeld, thanks for going on that website. We do have an Office of Compliance that is specific -- one of the functions of the Office of Compliance is to target inappropriate device labeling, and it looks like one of our homework assignments post this Panel will be to look into this -- the advertising for this particular device field.

But in a more general context, let's go back to several of the comments that we've heard, beginning with Dr. Brinker. I think there's perhaps a Panel consensus or urging that this whole device field be more appropriately labeled in the year 2012. And, certainly, when we get into our questions, specifically Question 3, we can delve into that in more detail.

And once a device field is more appropriately labeled, then it allows our Office of Compliance to more easily do its job when there are specific circumstances that really represent inappropriate advertising.

DR. YANCY: Thank you, Dr. Zuckerman. We appreciate that insight.

Let me request that each Panel member open your folder and pull the document out that says Circulatory Systems Device Panel Agenda, December 5th, 2012. For your benefit, the questions appear beginning on page 4 of this white document.

At this time, we need to focus our discussions on these specific FDA questions. I want to remind the Panel that this is deliberation period now amongst the Panel members only. Our task at hand is to answer the FDA questions based on the data in the Panel packs, the presentations we heard this morning, and the expertise around the table. In general, this means we can no longer reach out to FDA for clarification.

Let me be certain, then, that there are no further specific questions you have for FDA.

(No response.)

DR. YANCY: Seeing none, we'll proceed.

So in that context, with each Panel member who opts to respond to the questions that are presented before us, you will need to identify yourself to facilitate capturing your comments and to have an accurate record by the transcribers.

Let's begin. And at this point, if we can take a look at the first question. This question will be read aloud for the purposes of entering into the record.

DR. WU: Again, my name is Changfu Wu. I'm the lead reviewer for this Panel.

So FDA Question No. 1: FDA has identified the following risks to health for ECP devices based on the input of the original classification panel, review of industry responses to the 2009 515(i) order, the MAUDE

database, and FDA's literature review.

Risk No. 1, cardiac arrhythmia;

Risk No. 2, trauma to the limb;

Risk No. 3, ineffective cardiac assistance;

Risk No. 4, failure to identify the correct patient population.

Is this a complete and accurate list of the risks to health presented by ECP devices? Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risks should be included in the overall risk assessment of ECP devices.

DR. YANCY: Thank you. We've all heard the first question. Let me remind you that this Panel really is an advisory council. And the FDA will act based on our input, but not solely on our input, and put things in context so we feel as if we have the freedom to express our opinions.

And the other thing just by way of clarification, I will have to reserve my opinions to the end of the comments. So we'll need to go with Panel members first. Want to be certain that everyone has a chance to comment.

I think this first question is fairly straightforward, so hopefully, several people can frame the opinions of the Panel very crisply and quickly.

(No response.)

DR. YANCY: Hopefully several people can frame the opinions of the Panel.

Dr. Kandzari?

DR. KANDZARI: Thanks. I think that this fairly descriptively represents the proposed risks of the therapy. But that said, I would ask FDA perhaps to more carefully craft the fourth item of identifying the correct patient population because that's a fairly broad statement, and to me, it doesn't describe -- are you representing the idea that perhaps it's -- whether it's what we've talked about, heart failure, peripheral arterial disease, angina, refractory angina, or what we didn't discuss extensively but what was brought up is that there are a number of potential contraindications to this therapy that really are not elucidated by the evidence or by anecdote. We've talked about uncontrolled hypertension, arrhythmias, rapid heart rates, heart failure. So to me, this fourth element of failure to identify the correct patient population could represent the broad indications of peripheral arterial disease or more specific contraindications for patients even with refractory angina.

DR. YANCY: So, Dr. Kandzari, that was really an excellent summary. Are there members of the Panel that either want to expand upon what Dr. Kandzari indicated or say something differently?

Dr. Naftel?

DR. NAFTEL: So I'm just a little bit confused. I think there's a little bit of a logic problem here. It says these are the risks. I think the top three are risks. The failure to identify the population, that's -- I think it

needs to be couched a different way. Are you saying that -- because I'm thinking at a per-patient level. So are you saying that a patient in some subgroup might have different risk than patients in other subgroups? Like, I don't think you've got quite your outline right here because that's -- the fourth thing is not a risk. I'm looking for events here. It's --

DR. YANCY: So, David, in the spirit of what we're doing now, that would have to represent a standalone comment. FDA really is resorting to us now, and so we can just simply make the observation that Dr. Kandzari said, that we don't believe that the fourth item belongs with this set of statements, and maybe we need to do a callout and make a separate statement --

DR. NAFTEL: Okay.

DR. YANCY: But the question before us is to determine if all four of these, several of these or none of these are in keeping with the spirit of the question. Does that help?

DR. NAFTEL: Yes, then may I continue --

DR. YANCY: Please.

DR. ZUCKERMAN: Dr. Yancy, do you mind if Dr. Wu just clarifies that fourth bullet a moment?

DR. WU: Yes, the intention of the fourth risk is this. I think Dr. Naftel alluded to that. So it is for this -- the device functioned as designed, but for a subgroup of patients, for example, patients with the

congestive heart failure and -- because over half of the patients reported in MDR have CHF -- so for this particular subgroup patient population, just an example, so the events rate is high. So we need to, as I stated in my presentation, we want the sponsors to highlight the adverse events in the labeling so that the patients, the physicians can be better informed and make a correct decision.

DR. YANCY: Let's continue this discussion. Dr. Yuh?

DR. YUH: You know, I think that fourth bullet really reflects on the poor quality of the data. I mean, it's kind of a catch-all, isn't it? It seems to me it would be more useful to, for example, given that half the MDRs resulted in patients with heart failure, they should say patients with heart failure or left ventricular ejection fraction specifically below a given number agreed upon by consensus should be in that specifically, as opposed to kind of this catch-all with failure to identify the correct -- I mean, we don't even know how it works. So, you know, I'm not sure that that is going to be a very useful, without further clarification, special control.

DR. YANCY: So with that in mind, let me pose something to the Panel just to frame our conversations. Is there anyone who has any disagreement with the listing of cardiac arrhythmias, trauma to the limb, and ineffective cardiac assistance as risks to health for ECP devices?

(No response.)

DR. YANCY: So then let's discuss specifically about this fourth

bullet and identify if this is a risk or should it appear separately as a statement of contraindication.

Dr. Cigarroa?

DR. CIGARROA: So I'm having a bit of difficulty reconciling in my own mind the issue of whether or not as a risk heart failure should be called out. We have yet another small trial, the PEECH trial, that has a positive outcome. Yet for the treatment of angina, we have that as an exclusion criteria, and we have a number of reports of decompensation of heart failure during active treatment. And so given that, I think that it merits further discussion amongst the Panel, and I remain concerned about that specific subgroup, apart from item number four.

DR. YANCY: Would that be accomplished if it were stated as a contraindication independent of what we determined about number four?

DR. CIGARROA: I think that would go partially to addressing that concern.

DR. YANCY: Additional comments or discussion here? Dr. Somberg?

DR. SOMBERG: I think point four is fair. If you based your decision that this is a very safe device but has minimal benefit, you want to target the people who have that minimal benefit. If you don't, you will have no benefit, and then there are some risks of the device; specifically, it's afterloading. So just put your -- and in some ways, this -- put in anybody

who you think having 35 hours of afterloading therapy for a bit of time, severe hypertension, maybe some people with poorly compensated heart failure, maybe people with aortic regurgitation who are poorly compensated, et cetera. So I think that is a good catch-all when we have so little data and we're all hypothesizing.

DR. YANCY: So at the current time, we have three prevailing opinions. One is to dismiss this because it's nebulous in nature as a catch-all, isn't in keeping with the other three. The second is to keep it because it is a catch-all and allows for the capture of other considerations. And a third is to distinguish it from the others vis-à-vis procedural risk versus risk by indication. So we have three options on the table.

Dr. Allen and then Dr. Ohman?

DR. ALLEN: I guess I don't want to interpret what the FDA is saying, but I actually think it is appropriate up there because when I read this, what I'm hearing from the FDA is that it is a risk to use this device in, for example, the treatment of venous stasis disease, because the use of this device in a manner that may have gotten approval through the years may preclude that patient from getting appropriate standard of care for that treatment or for that disease process. And so when I look at that, failure to identify the correct patient population is a risk of the device, because if you inappropriately use this device in the wrong patient population, you may deny that patient appropriate therapy. Is that what the -- I don't want to

interpret what you were saying, but that's what I hear from you when you put that up there, and that's why I think it should stay.

DR. WU: For the general patient population, that was one of the factors that we considered.

DR. ZUCKERMAN: Yes, so the answer is we were looking at it from the holistic treatment pathway that you are, Dr. Allen.

DR. YANCY: So we need to bring this to some closure.

Dr. Ohman, you had a comment you wanted to make?

DR. OHMAN: Yeah. I think this fourth bullet can be clarified if it could be noted that patients that were excluded from the trials of the randomized trials that were controlled because it's a nebulous statement, but I think what you're getting at is two aspects, and one being the more appropriate use of other therapies, but in this statement is also the fact that if you had -- if you were on Coumadin and your INR was over 2.5 if I remember rightly from the PEECH trial, then you really couldn't be treated.

So there are statements in here that really should be added, I think, and they could be pooled together from the exclusion criteria from the trials. And they're pretty clear.

DR. YANCY: The dilemma, of course, is that this is by indication, because if you're thinking of coronary disease, then there was an exclusionary criterion for low EF, but if you're thinking about heart failure, that was an inclusion criterion. So we have to be very thoughtful about that

construct.

DR. OHMAN: I agree. So there's that duality.

DR. YANCY: Yes.

DR. OHMAN: But I think it can be done.

DR. YANCY: Oh, I would agree.

I would like for someone from the Panel to suggest a strategy that can resolve this, and you'll need to lead with your name, please, so we can capture that on the record.

Dr. Brinker?

DR. BRINKER: So I have just a comment before you were going to get there. And I think that there are a couple different issues. At first, I hated this fourth definition because I didn't see it as a risk. But I'm growing more fond of it as the discussion has gone on. It encompasses a lot of things. But one thing I think it should do, or we might think about, in most devices that are predicated, have labeling that are predicated on the clinical trials that define them, a statement is made that these trials were done in patients without this, that, or the other thing, or patients with this, that, and the other thing were excluded. And that's different than a contraindication. I think there are clear contraindications to the use of this that should be stated in the labeling, as should that separate comment, to show what the experience has been.

So in that way, I like this comment. And it may be that

patients with angina and heart failure may not be necessarily excluded. We don't have the kind of numbers to make that differentiation. And we don't know, as I think you've said before, the exact clinical background of the patients that are -- were cited in the MDR.

So I like this as it is with an understanding that in the labeling there'll be some -- that efficacy was established in trials which excluded patients with blank, blank, blank, blank, blank, and also in those situations which can be identified as clear contraindications.

DR. YANCY: So, Dr. Brinker, what I hear you and Dr. Ohman saying is that if bullet four remains, that it would be accompanied by a subtext that clarifies which patients have been studied previously, with the implication that patients not consistent with that profile reflect those who might be at risk?

DR. BRINKER: Yes.

DR. OHMAN: I like that.

DR. YANCY: Dr. Somberg?

DR. SOMBERG: I'm going to move what you said, that we accept the following risks have been identified and that bullet point four be clarified to -- I can paraphrase what you say, but I mean, it's in the record.

DR. YANCY: So, Dr. Zuckerman, with regard to Question 1, the Panel generally believes that the list of risks, specifically cardiac arrhythmia, trauma to the limb, and ineffective cardiac assistance are, in fact,

appropriate based on the review done by the FDA and the discussion held by this Panel. The Panel believes that the fourth bullet, failure to identify the correct patient population, requires further clarification and development, perhaps including either a subtext or additional commentary that would indicate which patients have been studied and which patients, by inference, have not been studied so that it's clear that there are uncertain risks in those that haven't been studied well.

DR. ZUCKERMAN: Thank you. That's quite helpful.

DR. YANCY: Great. If there are no other comments about that, we'll move on to FDA Question No. 2.

DR. WU: FDA Question No. 2: As defined in 21 C.F.R. 860.7(d)(1), there's reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and the conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. In addition, as defined in 21 C.F.R. 860.7(e)(1), there's a reasonable assurance of effectiveness if there are clinically significant results in a significant portion of the target population when the device is used for its indications for use and the conditions of use, when accompanied by adequate directions for use and warnings against unsafe use.

The FDA believes that the available scientific evidence

supports an adequate assurance of safety and effectiveness of ECP devices for treating chronic stable angina that is refractory to optimal antianginal medical therapy and without options for revascularization.

Do you agree that the available scientific evidence is adequate to support the safety and effectiveness of ECP devices for this indication?

Do the probable benefits to health from use of the ECP devices for this indication outweigh the probable risks to health?

DR. YANCY: Thank you for reading those questions into the record.

This is a discussion that we preempted during our internal deliberations, and now we need to provide guidance to the FDA. I know that Drs. Cigarroa and Somberg believe that the evidence is inadequate to support safety and effectiveness of ECP for the indication, specifically that of treating chronic stable angina, while several others -- I think Dr. Allen being one, Dr. Lange being another -- felt that there was a reasonable threshold -- I hesitate to say evidence -- to support the safety and effectiveness of ECP devices.

So since I know those opinions, let's start by gathering opinions from others, and then we'll go forward, unless I misrepresented you.

DR. CIGARROA: One small clarification. I believe it is safe, with the appropriate exclusions. I simply don't believe that for the targeted

audience, specifically refractory angina on optimal therapy without options for revascularization, efficacy has been demonstrated. I'm not worried about safety.

DR. YANCY: So I think we did capture your opinions, and I appreciate the clarification.

Dr. Lange?

DR. LANGE: Just for the record, that patient population was addressed from the Casey study, not the MUST-EECP trial. Twenty-eight patients with those criteria, randomized -- had an ECP versus 14 that didn't, and that did show effectiveness in terms of all the anginal outcomes measure, but not in the MUST-EECP trial. So just for the record.

DR. YANCY: So a study of 42 patients specifically addressed the new statement that we're considering.

Others whom we've not heard from with a thought on this very important Question 2a? Do you agree that the available scientific evidence is adequate to support the safety and effectiveness of ECP devices for this indication?

Dr. Hirshfeld?

DR. HIRSHFELD: Yeah, I've been modifying my thoughts about this as we've engaged in this discussion this morning. And I go back to Dr. Baron's slide 39 and 40, which is really the summary of the clinical evidence. And that's really the MUST-EECP trial. And she characterized this,

I think, quite accurately as a signal of efficacy. And what she pointed out was that the physiological trials have shown two physiological outcomes, namely the change in coronary collateral flow and the change in time to ST segment depression on the treadmill, neither of which are really clinical endpoints in terms of a patient's quality of life.

The patient's quality of life data, which I think are the clinical endpoints that one would expect to hold a treatment to, are the treadmill time, which was not statistically significant, and the change in angina counts, which was statistically significant.

So I think when we come right down to it, using clinical endpoints for efficacy here, the only piece of data that really supports this at a level of rigor that FDA ordinarily calls for is the change in angina counts.

DR. YANCY: My interpretation of your comments, Dr. Hirshfeld, is that you are somewhat tentative about Question 2a, but the balance of your opinion is in favor of it?

DR. HIRSHFELD: No, I don't think that's accurate. I think as I've listened to these discussions today, I'm getting progressively less enthusiastic that real clinical efficacy that makes a difference for the patient's quality of life is not demonstrated.

DR. YANCY: So does declining enthusiasm mean yes, no, or maybe?

DR. HIRSHFELD: I think I'm drifting to no.

DR. YANCY: Dr. Lange?

DR. LANGE: Again, I don't want to -- and I'm not trying to convince anybody, but there were four randomized controlled trials, only one of which addressed the patient population that the FDA is referring to. That's the Casey trial. In the MUST-EECP trial, there were no Class IV anginal patients at all. But the Casey trial, conducted in Florida, was done with 42 patients that all met the criteria. It is admittedly a small study. I'm not going to try to convince anybody about its -- whether you agree or not, but that's the only trial cited by the FDA that applies to these patients in a randomized controlled trial fashion.

DR. YANCY: Let me go to Dr. Slotwiner and come back to Dr. Cigarroa.

DR. SLOTWINER: I'm trying to balance the risks and benefits and the very small population for whom this would be used under this indication. And I think thinking that there would -- are very few alternatives for this very sick group of patients, I think even though the signal is weak, there are several indications that it's present. And I think that because the risk is so low, I would favor keeping it as an option for them. So I would favor it as remaining as an indication and accepting that.

DR. YANCY: So at present, I have Drs. Lange, Slotwiner, and Allen as being in favor, with all the apparent provisos of keeping the language that we see -- that is, a yes. And I have Dr. Hirshfeld, Dr. Somberg,

and Dr. Cigarroa as a no. So let me hear from someone other than these members and go forward. Dr. Cigarroa, I promise to get to you next, though.

Dr. Brinker?

DR. BRINKER: Put me in the yes column. I think that there is this population of patients in which there is truly no -- nothing else to offer. I've sent patients through this therapy myself. I'd hate to have it removed even though I don't understand the physiology. It's not an afterload increaser if it's applied right. It's an afterload decreaser. It's a preload increaser. And I don't think it's another intra-aortic balloon that has lasting effects. I think it's -- whatever it is, it's entirely different. If all it did -- and I hate to say this in this audience -- but if all it did was supply physical activity and had a placebo effect in this particular group of patients, that could be a very meaningful change in their life. So I'm willing to endorse the indications as listed as being supported.

DR. SOMBERG: Can I just suggest a clarification?

DR. YANCY: Just a minute, please. Dr. Doty was next.

DR. DOTY: So I think my perspective, I'll go in the yes column with Dr. Brinker, because we're looking at a reasonable assurance, and Dr. Baron gave us some data on slide 45 reminding us the American Heart Association and ACC classification remains Class IIb recommendation. That's 2012, so I think that's a body of information from expert reviewers that supports this is a reasonable therapy.

DR. YANCY: Thank you very much.

Dr. Dehmer?

DR. DEHMER: Yes, and I too will go in the yes column for this, favoring the side of the guideline writers, who I'm sure very carefully thought this through before making their recommendation. I don't have a lot of personal experience with this, but I have enough to know that I have seen it work in a few very selected, appropriately selected individuals. I agree we don't know exactly how it works. There was one fairly carefully done study that did show it increased coronary collateral blood flow. I think we've seen, again, not randomized, well-controlled trials, but we've seen improvement in myocardial perfusion after a course of this therapy. And those are things that are somewhat hard to fudge, if you will. So you can put me down on the yes column. Clearly, it's safe. And I believe in well-selected, appropriately selected patients, it is effective.

DR. YANCY: It's interesting that we've made reference to the ACC/AHA guidelines, a major component of my professional time now, just like with Dr. Ohman. I want to remind you of the vernacular that is required when an indication is IIb. It means "probably effectiveness" or "usefulness is uncertain." So it captures the tentativeness of the committee, but nevertheless it is a statement that it is a probably reasonable thing to do.

And I get the feeling that those in the yes column are of that mindset. I think that's what Dr. Brinker is suggesting.

Dr. Yuh?

DR. YUH: Yes. If you read that question explicitly, it asks if there's scientific evidence that's adequate to support, not necessarily establish or confirm, and I think the objective as well as subjective evidence, you know, supports a yes from me, at least, in that.

DR. YANCY: Dr. Somberg, I'd like to get back to you. You had a question. And I wanted to get opinions from others. So forgive me for going on.

DR. SOMBERG: No problem. It's not a question or an opinion. I think it should be clarified, though, that the issue is not whether the device not be available or be available. It's a question of whether there will be a call for information or whether it's down-classified to II whether -- and then from here and henceforth any other sponsor can get approval by specific controls, not needing any more clinical data.

So that's the question. So I think Dr. Brinker, when you said "I don't want to take it away" -- maybe I'm mischaracterizing -- or "I don't want to see it withdrawn" or something, that's not the issue today. The issue is how you would get a supplemental information or whether there's no further supplemental information needed for approval. Am I correct on that, Dr. Yancy, of what the question is? It's not whether we're going to take it away or not. That's not a decision here, to withdraw it from the market. The decision is how one might subsequently get another device approved or

how the manufacturers are going to justify whether it stays on the market or whether additional information is needed.

DR. YANCY: So I think that was the purpose of the FDA comments that opened our post-break session, indicating that anything within the 510(k) space is, if you will, a predicate set of data points that another device can leverage, whereas anything within the PMA space is proprietary and is for that specific device. How a PMA initiative as a result of these deliberations will influence a de novo application will be very interesting, that is, whether or not that application would follow the Class II indications or follow the Class III indications. And I suspect that would be device-specific. That is, if a new ECP device comes forward and we split these classifications, it would depend on which indication was being sought.

But I think for complete clarity on this, I'd ask Dr. Zuckerman to give us just a moment of input here.

DR. ZUCKERMAN: Okay. I think what folks are worried about is if this device stays Class III and there is a call for PMAs, potentially, FDA has the option within a specified period of time to take these devices off the market if we don't get appropriate data, et cetera.

But weighed against that, I think the Agency would be very sensitive to the fact that an appropriate indication for this device to study would be no-option patients, meaning patients with significant angina who are not felt to be revascularization candidates anymore for reasons A, B,

and C. And, therefore, there would be an appreciation that this is a last-option therapy. And our general approach would be to work with sponsors just to make sure that we get the appropriate data in a reasonable timeframe.

So I wouldn't necessarily perseverate on the idea of having these devices taken off the market as a first step, given the public health implications of this particular niche patient population which is significantly ill.

DR. YANCY: Dr. Katz?

DR. KATZ: I guess my question, then, is would requiring a significant study from five manufacturers that are dealing with 20,000 patients a year de facto take it off the market because the cost of doing the study would then not be worth anyone's time? It may not be a question for us directly, but that may be the result of a decision that we make.

DR. ZUCKERMAN: Again, regardless of the Panel's decision here, I think there's an appreciation on the part of the FDA that we try to develop studies that are doable and least burdensome. And as Dr. Ohman indicated, we wouldn't be necessarily looking for a 20,000-patient mortality study. Certainly, if someone wants to do it, we won't deny it. And better yet, given the importance of this patient population, we could also employ Panel members to help us facilitate the process. So, again, I don't think that removal of the device is the key problem that we're faced with today.

DR. YANCY: Let me do this to keep our time sensitivities intact. Are there any members of the Panel that believe we need to have separate deliberations about Question 2b? Do you believe that the opinions we've already expressed are appropriate for 2a and 2b? I have enough affirmative head nods around the table.

I am ready to formulate a response unless there is a new statement that someone wants to make about these two questions in Question 2.

Dr. Brinker?

DR. BRINKER: Just a clarification, Bram, because what you just said is interesting, and it backs off of the FDA official proposal, if I understand it correctly. So if you endorse a trial looking at the specific indications that Rick has said has already been justified in a small group of patients, but you -- if there's a feeling that needs to be done in a larger group of patients, that could be done without reclassification -- it could be done by saying it's Class III for all indications and this is what you need to do for the chronic angina. Or could it be done with the division and a suggestion that the study be done to justify this?

In other words, if we take the latter, say that there's not verdant and robust evidence that in this particular high-risk, no-option patient population that it's beneficial even though there are all these other signals that it may be, then you're saying, really, I think, that we should keep

it a Class III unless you can tell me a way around that.

DR. ZUCKERMAN: No, I was just pointing out several options. And, again, we're here to listen to an independent Advisory Panel. The Agency has just put one option on the board as a straw -- because we've tried to do due diligence and suggest this is a reasonable pathway. But you know, one option is to keep it as a PMA Class III and ask for additional clinical trial evidence that way. Another option that I think you were alluding to, Dr. Brinker, is to go with the FDA's suggestion. It would be Class II, but people recognize, I think, that there's a dearth of evidence in this field, and regardless of FDA classification, we need more trials for the angina indication. And if the sponsors want to do that to hopefully enlarge the scientific space, and hopefully they're incentivized by clinicians who want more data, that's a doable prospect that won't include any FDA IDE, et cetera; you're just gathering more data within the labeled indication.

DR. YANCY: So before I respond directly to the question, let me just remind the Panel. I have collected 10 responses. Adding the Chair's response, I have 11 responses now. Eight responses are weakly in favor of 2a, 2b, and three responses are opposed. I just want to be very clear on the yes and noes before we generate the language. Is there any discussion? Is that capturing the flavor of the committee; that's over 70% are saying weakly yes, and 3 are saying no?

DR. KANDZARI: In short, yes, but for 2b, you specifically asked

if we had any further comments. And I'll raise this issue for the Panel to consider. I've been thinking about 2b, in particular, in the context of other therapies that were considered last-option resorts a few years ago. And two that in particular come to mind are pentoxifylline for peripheral arterial disease claudication and chelation therapy. And those are two therapies that since large randomized trials that were demanded by the clinical community and not by any regulatory mandate have since been proven negative. And if I were to ask that same question, 2b, to those therapies, though, I'm not sure that five years ago, prior to those randomized trials, we could say that those therapies had probable benefits that outweighed possible risks.

Here I think the risks are very low. The threshold for approval, given that this is an end-stage population with limited other therapeutic alternatives, also motivates me to say yes. I think we all recognize who vote yes that this is not necessarily the best-studied indication among subgroups or limited trials of less than 50 patients, but that the probable benefits directionally outweigh those risks.

DR. YANCY: So, Dr. Kandzari, I think the point that you make nicely is that independent of the FDA process, there are other approaches that can allow the acquisition of new data points especially in an era of comparative effectiveness research and, in particular, with an ongoing registry that is capturing real-time information not yet having full clarity on

all the data fields. And so I think your point is well positioned.

We need to make a response to the FDA question. Briefly, Dr. Hirshfeld?

DR. HIRSHFELD: Yeah, I'd just like to clarify my position. I think that history has actually shown that there has not been a randomized clinical trial of the efficacy of this procedure for quite some time. So it looks as though there's currently no incentive in industry or academia to launch such a trial. The evidence that we have for an efficacy signal is very weak. And I'm concerned that if some regulatory force does not require an objective demonstration of the actual efficacy of this technique, we'll never get the answer.

DR. YANCY: One could also take a pragmatic approach and say that there just might be a natural history to this treatment that inclines it towards obsolescence as time goes on, and that may be yet another outcome here.

Let me attempt to formulate a response on behalf of the Panel to Question 2. And this is for Question 2a, 2b, with the caveats as noted by Dr. Kandzari.

In response to Question 2a and b, Dr. Zuckerman, this Panel generally believes that the evidence to support the indication for ECP for chronic stable angina is weak and the database is lacking. Nevertheless, we see no reason to not support the ongoing use of this device for these specific

indications and especially as outlined by FDA for those patients who are refractory to all other interventions.

This Panel also believes, and this is reflecting on the majority opinion, that this is a very low-risk device, and this modest benefit that apparently is there is sufficient that those benefits outweigh the risks to health.

DR. ZUCKERMAN: Thank you. Because this is such an important question, is there any Panel member who wants to have a final comment on what Dr. Yancy just said?

(No response.)

DR. ZUCKERMAN: Good.

DR. YANCY: Thank you. And my thanks to the Panel. I recognize this was perhaps the one that required the most thought and consideration, and I respect the divergent opinions of Drs. Somberg, Cigarroa, and Hirshfeld in this discussion.

Question 3, please?

DR. WU: FDA Question No. 3: FDA believes that the following special controls can adequately mitigate the risks to health for ECP devices for treating chronic stable angina that is refractory to optimal antianginal medical therapy and without options for revascularization and provides sufficient evidence of safety and effectiveness:

1. Non-clinical performance evaluation of the device must

demonstrate a reasonable assurance of safety and effectiveness for applied pressure synchronization of therapy with the appropriate phase of the cardiac cycle and the functionality of alarms during a device malfunction or abnormal patient condition;

2. Reliabilities of the mechanical and electrical systems must be established through bench testing under simulated-use conditions and matched by appropriate maintenance schedules;

3. Software design and verification and validation must be appropriately documented;

4. The skin-contacting components of the device must be demonstrated to be biocompatible;

5. Appropriate analyses and testing must be conducted to verify electrical safety and electromagnetic compatibility of the device;

6. Labeling must include a detailed summary of the device-related and the procedure-related complications pertinent to use of the device.

Do you agree that these special controls are adequate to mitigate the risks to health for ECP devices for chronic stable angina and provide sufficient evidence of safety and effectiveness?

Please comment on whether you disagree with inclusion of any of these special controls or whether you believe any other special controls are necessary.

DR. YANCY: This Question 3 is open for discussion.

Dr. Ohman?

DR. OHMAN: Yeah, so I believe here would be a nice place to, as to bullet 7, I guess it would be, to have a labeling for relative and absolute contraindication based on the clinical investigations that have been carried out. I'm not going to specify exactly what's in those issues because I think you need to search the literature for that, but I think it would be very helpful here because that goes back to the fourth bullet from the previous thing we voted on, and it would allow us to sort of nicely separate out this what is truly the right population or semi-right population.

DR. WU: Can I make a comment?

DR. YANCY: Yes, sir.

DR. WU: So contraindication is considered to be a general control. It will be in the labeling if it's appropriate. So that's why we didn't list it as a special control.

DR. OHMAN: Okay. Maybe I need an education on what's the difference between a general and a special control --

DR. ZUCKERMAN: Okay, Dr. Ohman. If we understand the gist of your comments and the comments from other Panel members like Dr. Brinker, and we really need a good discussion here, I think you would like the FDA to develop really appropriate standardized labeling which has an appropriate indication, contraindications, warnings, precautions, good

clinical data section. As you and others have pointed out right now, the labels are haphazard, and I think you feel that the FDA and industry has to get our act together to get a standardized label here. I don't want to put words in your mouth.

DR. OHMAN: Correct.

DR. YANCY: So you did put words in his mouth.

(Laughter.)

DR. YANCY: Dr. Naftel?

DR. NAFTEL: So I'm agreeing with this list of controls. It sounds very reasonable to me. But I'm looking at the introductory sentence, "FDA believes the following controls can" -- and then skip on down -- "can provide sufficient evidence of safety and effectiveness." So I don't get that part of it, because these controls are more manufacturing and all. It's nothing to do with patient outcome or information. So I don't see where these controls tell you anything about safety and effectiveness. They may mitigate, and I think that's what you're trying to do. But there's nothing in here about safety and effectiveness.

DR. YANCY: I think that's an excellent point, actually. And that is something --

DR. NAFTEL: I'm not saying that's bad.

DR. YANCY: But that is something this Panel can take under advisement. We can direct the FDA that we believe that the list is correct

with the inclusion of some specific mention, as Dr. Zuckerman and Ohman just discussed, about indications and contraindications and with the exclusion of the phrase "and provide sufficient evidence of safety and effectiveness."

Yes, Dr. Greenfield?

DR. GREENFIELD: I would just like to revisit, briefly, the issue of safety. I think these devices are inherently relatively safe, but I would caution the Panel to rely very heavily on the numbers reported. When the OIG looked at the relationship between MDRs under the FDA and what is happening in the rest of the world, the estimate was the FDA sees about 5% of what is actually going on. So the fact that they're a large number of use and a relatively small number of reports doesn't necessarily mean that these events are not happening; they just are probably not being reported.

DR. YANCY: Thank you, Dr. Greenfield.

So without anyone else -- yes, Dr. Brinker?

DR. BRINKER: I think that the purpose of this Question 3 is a statement that allows it, I believe, to be bifurcated into the Class II range. And that is the acknowledgement that non-clinical standards can set a bar for safety and efficacy since we know what the clinical outcomes are. And I think that this is jargon that says that these things will be done to make sure that the product is made within the proper set of guidelines with the proper attention to things like software to make sure it's not inflating

inappropriately and all these other things that we've listened to.

So within that group, it's the closest thing you can get to an assurance from a structural point of view without clinical data for safety and efficacy, although I realize that this in itself doesn't declare safety and efficacy.

DR. YANCY: So to be clear -- and I think you make a very good point, Dr. Brinker, that this is the difference between general controls, which is a Class I, and special controls, which is a Class II, but with the consideration raised by Dr. Ohman that even though contraindications typically fall under general controls, there is some angst that additional commentary appear here under these special control circumstances to further qualify this technology.

Dr. Hirshfeld?

DR. HIRSHFELD: Yeah, I would actually submit that this stuff is actually general controls, heavy, and it's all about basically good manufacturing practices and device quality which is linked to device safety, but it says nothing about device efficacy.

DR. YANCY: So that's a second opinion along with Dr. Naftel, that the closing phrase, "and provides sufficient evidence of safety and effectiveness," is ill-placed; is that correct? Is that how you'd want to --

DR. HIRSHFELD: I could be perfectly happy with the statement as long as it didn't comment on effectiveness. I think these are qualities

which relate to safety, but they don't relate to effectiveness.

DR. YANCY: So another good point.

Yes, Dr. Brinker?

DR. BRINKER: Just a second of rebuttal. So I think that if you assume that the device as we've looked at it today is safe enough and effective enough to be approved, these things ensure that they will maintain that. And for additional kinds of -- additional entries into the market, if they meet this, it'll be assumed that it'll be safe and effective. I think that's what this is. Maybe I'm wrong.

DR. YANCY: So Dr. Zuckerman?

DR. ZUCKERMAN: No, I just want to underline that I think Dr. Brinker has gotten to the heart of it. When you go to Class II with special controls, there is the implicit assumption, as Dr. Brinker has indicated, that the general class of devices has appropriate safety and effectiveness data, however marginal it may be in this case, and therefore, we are developing primarily a preclinical construct that will allow us to make sure that the next device that wants to come on the market is as safe and effective. But you need to buy into the construct that Dr. Brinker just mentioned.

DR. YANCY: Dr. Somberg?

DR. SOMBERG: I just want to say that I agree with the other people who said that this is not adequate for efficacy because, exactly, I don't believe that we have the efficacy data. And by down-classifying it, this

is all the data you will ever get in the future for any new device.

DR. YANCY: So I'm interpreting that, then, as a no vote to No. 3? Okay.

Dr. Slotwiner?

DR. SLOTWINER: I interpret the effectiveness as Dr. Brinker did, in this context as a special control. And I think my interpretation of it is that these are controls to make sure the device will function effectively mechanically. And so I support the statement as it is and the list.

DR. YANCY: So I'm interpreting that as a yes vote? All right.

Dr. Zuckerman, the Panel would like to respond to you with regard to Question 3 and indicate that, generally speaking, the majority of the Panel believes that the special controls highlighted in No. 3 are adequate to mitigate the risk to health for ECP devices for chronic stable angina, with two provisos that we would like the FDA to take under deliberation. One is the inclusion of at least the most important contraindications so that it is yet again apparent in these special controls. And the second is to revisit the comments that address effectiveness in the context of the marginal data to support effectiveness at the outset.

DR. ZUCKERMAN: Okay. Thank you.

DR. YANCY: Thank you. And thanks to the Panel.

Let's move on to Question 4, please.

DR. WU: FDA Question No. 4. Although they appear to be safe

for use, FDA believes that the effectiveness of ECP devices used to treat all other indications (i.e., non-chronic stable angina indications, such as unstable angina, acute myocardial infarction, cardiogenic shock, and congestive heart failure, etc.) is not well established. FDA bases this determination on the lack of sufficient evidence to support the effectiveness for these uses, and therefore, FDA does not believe that special controls can be established to assure the effectiveness of ECP devices for these indications.

a. Do you agree that the available scientific evidence is not adequate to support the effectiveness of ECP devices for indications other than chronic stable angina?

b. If you do not agree, please discuss the following:

    i. The scientific evidence available in support of the effectiveness of ECP devices for any of the non-chronic stable angina indications.

    ii. Special controls that you believe would be sufficient to assure effectiveness of ECP devices for any of the non-chronic stable angina indications.

DR. YANCY: So as a point of clarity, if the response by the Panel is affirmative to 4a, then, de facto, 4b requires no comment. So let's first address 4a.

Dr. Lange?

DR. LANGE: 4a, yes; b, n/a.

DR. YANCY: Dr. Dehmer?

DR. DEHMER: I agree with Dr. Lange.

DR. YANCY: Are there any divergent opinions?

(No response.)

DR. YANCY: So, Dr. Zuckerman, this Panel believes that in response to Question 4, that the answer is yes for 4a, that the available scientific evidence is not adequate to support the effectiveness of ECP devices for indications other than chronic stable angina and, thus, the questions put forward in b are not applicable.

DR. ZUCKERMAN: Thank you.

DR. YANCY: Question 5, please?

DR. WU: FDA Question No. 5: 21 C.F.R. 860.93 describes the classification of implants, life-supporting or life-sustaining devices, and states that "the classification panel will recommend classification into Class III of any implants or life-supporting or life-sustaining device unless the Panel determines that such classification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. If the Panel recommends classification or reclassification of such a device into a class other than Class III, it shall set forth in its recommendation the reasons for so doing."

The original classification panel for ECP devices indicated that

ECP devices were life-supporting; however, FDA does not currently agree with this recommendation from the original panel.

a. Would you consider ECP devices to be life-supporting?

b. Based on the available scientific evidence and the proposed special controls, what classification do you recommend for:

   i. Chronic stable angina that is refractory to optimal antianginal medical therapy and without options for revision; and

   ii. All other intended uses?

c. If the answer to part a. above is yes, in accordance with 21 C.F.R. 860.93, please discuss the reasons for your recommendation if you recommend a classification other than Class III for any of these indications.

DR. YANCY: Thank you. We will begin with deliberation of 5a. Depending on that deliberation, we may not need to respond to 5c. And then the most pertinent issue will be to discuss 5b(i) and (ii).

So as a Panel, do we consider ECP devices, external counter-pulsation devices, to be life-supporting?

DR. YANCY: Dr. Lange?

DR. LANGE: No.

DR. YANCY: Dr. Cigarroa?

DR. CIGARROA: No.

DR. YANCY: Dr. Brinker?

DR. BRINKER: No.

DR. YANCY: Are there any divergent opinions? Dr. Somberg?

DR. SOMBERG: This is a very interesting question. It was worded by an attorney, it looks like. If it wasn't life-supporting and life-sustaining, why would it be classified a Class III device in the initial situation? And then it would be a Class II. And why did we discuss Class III versus Class II? So I think these are semantic points here. No, it does not sustain life. No, it is not life-supporting. But yes, it is a device that has a major impact on an individual's health, and therefore its efficacy needs to be established through clinical trials. And the administering of it to a patient who does not have benefit from it would probably have an infinite harm base even though it's relatively safe, and therefore, it shouldn't be done.

So I think this doesn't speak to the clinical urgency of needing clinical information on these type of devices even though they may not be "life-supporting" or "life-sustaining."

DR. YANCY: Part of this question is to discriminate or even segregate the life-supporting nature of the device and its classification. So if we determine that it's life-supporting but yet as a Panel recommend it be reclassified as a Class II device, then we would need to provide separate justification for making that decision. The premise of our Panel meeting has been based on the previous approval as a Class III device using the 510(k)

approach, and that's part of what I understand we are addressing. But your comments are well made.

We have three votes of no and then one statement of clarity about the life-supporting nature of the devices. Are there any other comments or votes about this before we formulate a response to the FDA?

(No response.)

DR. YANCY: So, Dr. Zuckerman, with regard to 5a alone, the majority of opinion of this Panel is that we do not consider external counter-pulsation devices to be life-supporting.

DR. ZUCKERMAN: Thank you.

DR. YANCY: With regards to b, based on the available scientific evidence and proposed special controls that we've already discussed, what classifications do you recommend for (i) chronic stable angina that is refractory to optimal antianginal medication therapy and without options for revascularization and (ii) all other intended uses.

And just for clarity, the FDA has suggested a reclassification for the indication of chronic stable angina to a II and has suggested that the other indications remain a III, and the implication of that is a requirement for premarket approval.

This is open for discussion.

DR. ZUCKERMAN: Right. And could you just refer to slide 55 to help you on this discussion.

DR. YANCY: If we can place slide 55 back, Dr. Wu, that would be helpful. Thank you.

So this is open for discussion. Dr. Lange, please start.

DR. LANGE: I agree with the FDA's recommendation and support it.

DR. YANCY: Dr. Slotwiner?

DR. SLOTWINER: Yes, I agree with the FDA's recommendation as well.

DR. YANCY: Dr. Cigarroa?

DR. CIGARROA: Based on my response to the first question, I believe, therefore, that I disagree and that it should remain Class III. I remain concerned that one trial on 2:1 randomization in a single site potentially suffers from type II error and is difficult to extrapolate to this general American population.

DR. YANCY: So the record of our deliberations will indicate that you believe that for chronic stable angina, it should remain a Class III?

DR. CIGARROA: Thank you.

DR. YANCY: Dr. Dehmer?

DR. DEHMER: I believe that the FDA's assessment has been measured and thoughtful, and I agree with their assessment.

DR. YANCY: Thank you.

Dr. Ohman?

DR. OHMAN: I also agree with the FDA recommendation, and I think it's important to recognize when the Agency and the guidelines recommendations are aligned, that that actually is a fairly happy place for us to be in.

DR. YANCY: Happy place is a good thing. I'm not sure where my happy place is, but I'll give that some thought.

(Laughter.)

DR. YANCY: Dr. Somberg?

DR. SOMBERG: I support the statement of Dr. Figarroa [sic]. I would be a no.

DR. YANCY: So you and Dr. Cigarroa would both be a Class III.

Dr. Hirshfeld, for the benefit of the record, would you remain with the Class III designation as your vote?

DR. HIRSHFELD: Yes. And I'd just like to emphasize that my concern is that the clinical efficacy of this technique is not demonstrated and that I think that if it is classified as a Class II, we will never know the answer.

DR. YANCY: So three Panel members have indicated an intention or preference that for the indication of chronic stable angina, with all of the language suggested in the patient cohort, that this device remain a Class III. Are there others on the Panel who would vote that the device remain a Class III?

(No response.)

DR. YANCY: So that means that all others either would abstain or would be comfortable with reclassifying ECP as a Class II for the indication of chronic stable angina.

For all other intended uses, is there someone who either wants to make a motion or reflect your thought of the opinion of the Committee about what we should do with the other intended uses or previous uses of ECP as a Class II, that is, reclassification, or reconfirm a Class III so that for continued use it would require premarket approval?

Dr. Allen?

DR. ALLEN: I would move we follow the FDA's recommendations that it remain a Class III indication for all other --

DR. YANCY: Thank you, sir.

Dr. Katz?

DR. KATZ: I agree.

DR. YANCY: Thank you, sir.

DR. YUH: I agree.

DR. YANCY: Drs. Yuh, Katz, and Allen agree that for all other intended uses, the devices should remain a Class III, which means premarket approval would be required to continue marketing the devices for those indications.

Is there any divergence from that opinion?

(No response.)

DR. YANCY: So, Dr. Zuckerman, this Panel believes that for chronic stable angina that is refractory to optimal antianginal medical therapy without options for revascularization, a majority opinion would reclassify this indication for external counter-pulsation to a Class II. Three Panel members, specifically, Dr. Cigarroa, Dr. Somberg, and Dr. Hirshfeld believe it should remain a Class III.

For all other intended uses, the Panel is unanimous that the device should remain a Class III, and for continued marketing for those indications, it should require premarket approval.

And I would add as Chair, based on the notations made by Dr. Hirshfeld earlier, that some change in marketing behavior be considered.

DR. ZUCKERMAN: Thank you.

DR. YANCY: I'd like to thank the Panel. This completes our deliberations about the first objective today, specifically addressing external counter-pulsation.

We are reasonably in keeping with our schedule, but before we break for lunch, it's important that we document input from Mr. Burke Barrett, our Industry Representative, and from Ms. Debra Gates McCall, our Patient Representative.

I started with Ms. McCall the last time; I'll start with Burke this time.

MR. BARRETT: I have nothing further to add. Thank you.

DR. YANCY: Thank you, Burke.

Ms. McCall?

MS. McCALL: I also have nothing to add.

DR. YANCY: Thank you, again.

We are approximately 5 minutes ahead of time, so I appreciate the Panel's due diligence here. We will end this first session and break for lunch. Panel members, please do not discuss or contact anyone about the meeting topic during the break. This includes discussion even amongst ourselves or with any members inside or outside of the audience.

The first session of this December 5th, 2012 meeting of the Circulatory Systems Device Panel is now adjourned.

(Whereupon, at 12:25 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

December 5, 2012

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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ZACH E. DUNCAN

Official Reporter